Drug News
藥 物 情 報

Issue Number 54

This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in April 2014 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

Australia: Strontium ranelate (Protos) and risk of adverse events

On 3 April 2014, the Therapeutic Goods Administration (TGA) announced that Servier Laboratories (Australia) had updated the Product Information (PI) for strontium ranelate (Protos) after the completion of a TGA review. The updates to the PI, made in consultation with the TGA, emphasise the contraindications, reinforce precautions, highlight the need for regular monitoring and update data relating to the risk of adverse events. Strontium ranelate is used to treat severe osteoporosis, by increasing bone formation and decreasing bone loss. A black box warning had been added to the PI to highlight the updated information.

The black box warning states: "Protos should only be used when other medications for the treatment for osteoporosis are considered unsuitable. Protos is contraindicated and must not be used in patients with established, current or past history of: ischaemic heart disease, peripheral vascular disease, cerebrovascular disease, uncontrolled hypertension, venous thromboembolism, pulmonary embolism. It should also not be used in patients who are temporarily or permanently immobilised. Protos should be used with caution in patients with risk factors for cardiovascular events or venous thrombosis: hypertension, diabetes, smoking, hyperlipidaemia. All patients prescribed Protos should be fully informed of the risk of cardiovascular events and venous thrombosis. Patients should be regularly monitored, every 6 months."

In Hong Kong, Protos Granules for Oral Suspension 2g, (HK-53835) is registered by Servier HK Ltd., and is a prescription only medicine. Safety alerts regarding the cardiovascular risk, venous thromboembolism and severe skin reactions associated with strontium had been released by Health Sciences Authority (HSA) of Singapore and the European Medicines Agency (EMA) and were reported in Drug News Issues No. 23, 25, 29, 41, 42 and 51. The matter was discussed by the Registration Committee of the Pharmacy and Poisons Board in December 2012, September 2013 and February 2014. The Registration Committee decided that the registered package insert of Protos should include the appropriate safety information as outlined in Drug News Issue No. 51. Department of Health (DH) should remain vigilant on any new safety information of the captioned product announced by other overseas health authorities. In view of the completion of TGA's review, the information will be provided to the Registration Committee for further consideration. After reviewed, Servier has confirmed that they would update the package insert to include the final recommendations of the EMA.

Singapore: Updated warnings and precautions on visual field defects with the use of Topamax® (topiramate)

It was noted from the website of Health Science Authority (HSA) on 2 April 2014 that Janssen, a division of Johnson & Johnson Pte Ltd, would like to alert healthcare professionals to the potential risk of visual field defects associated with Topamax®. In double-blind, controlled monotherapy epilepsy trials, visual field defects were reported at a frequency of 0% to 1.3% in Topamax®-treated adult patients. Based on cumulative data from a recent review of post-marketing safety databases

and clinical trials, the package insert for Topamax® will be updated in Singapore to reflect new safety information and guidance on visual field defects. Healthcare professionals are advised to consider discontinuing Topamax® if visual problems occur at any time during treatment with this drug.

In Hong Kong, there are 23 registered pharmaceutical products containing the antiepileptic topiramate, and are prescription only medicines. DH had not received any adverse reaction report in connection with the use of the products, and will keep vigilant on any safety updates of the drug. In view of the HSA's recommendation, a letter to healthcare professionals to draw their attention and urge them to report any Adverse Drug Reaction (ADR) related to the drug was issued on 4 April 2014, and the matter will be discussed in the meeting of the Registration Committee.

Canada / Singapore: Association with liver problems with the use of Zelboraf® (vemurafenib)

On 7 April 2014, Hoffmann-La Roche Ltd. (Roche Canada), in consultation with Health Canada, informed healthcare professionals of important new safety information regarding the risk of Drug Induced Liver Injury (DILI) reported with Zelboraf®. Zelboraf® is indicated as a monotherapy for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma. DILI, including cases of severe liver injury, has been reported with Zelboraf®. The Zelboraf® Product Monograph would be updated to include appropriate information regarding the risk of DILI and physicians should discuss the currently available information regarding benefits and risks of Zelboraf® with their patients. Prescribers are reminded to monitor transaminases, alkaline phosphatase, and bilirubin before initiation of Zelboraf® treatment and monthly during treatment, or as clinically indicated. Liver injury should be managed using dose reduction, temporary interruption, or treatment discontinuation of Zelboraf®.

There were no reported deaths among the 63 cases of liver injury. There were two severe cases (based on the DILI severity index by the same Expert Working Group), both reported as hepatic failure; the outcome of one case of severe liver injury was reported as completely resolved with Zelboraf® discontinuation while the outcome of the second severe liver injury case is not available at this time.

On 23 April 2014, HSA also announced that Roche had informed healthcare professionals of the risk of DILI reported with Zelboraf® (vemurafenib) based on the above study. Healthcare professionals are reminded to monitor the risks of liver injury, as indicated in the local package insert for Zelboraf®.

In Hong Kong, Zelboraf Film-coated Tab 240mg (HK-61970) is registered by Roche HK Ltd., and is a prescription only medicine and indicated as an anti-neoplastic drug. The product insert of Zelboraf Tab in HK has already included special warning on liver injury associated with the use of vemurafenib, and the relevant precautionary measures. DH had not received any adverse reaction report in connection with the product, and will keep vigilant against any new safety updates related to the drug.

Singapore: Communication on the risk of severe skin reactions with Dilatrend® (carvedilol)

On 7 April 2014, Roche in Singapore informed healthcare professionals of newly emerged safety information for Dilatrend®. From a review of the cumulative data from the company's safety database, very rare cases of severe cutaneous adverse reactions such as toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) have been reported during treatment with carvedilol. The package insert for Dilatrend® will be updated with this important new safety information. Healthcare professionals are recommended to consider permanently discontinuing the use of Dilatrend® in patients who experience severe cutaneous adverse reactions possibly attributable to carvedilol.

In Hong Kong, there are a total of 27 carvedilol containing pharmaceutical products including Dilatrend Tab 25mg (HK-36984), Dilatrend Tab 12.5mg (HK-42821) and Dilatrend Tab 6.25mg (HK-42822) which are registered by Roche HK Ltd., and are prescription only medicines. They are indicated for hypertension, angina pectoris and symptomatic congestive heart failure. According to Roche, a letter to healthcare professionals had been

issued on 1 April 2014 to draw their attention to the issue, and would submit an application to DH to update the package insert of the products to include the relevant warnings and precautions. DH had not received any adverse reaction report in connection with the drug. In view of HSA's announcement, a letter to inform healthcare professionals to draw their attention was issued on 10 April 2014, and the matter will be discussed in the meeting of the Registration Committee.

Canada: Association of Neupogen® (filgrastim) and Neulasta® (pegfilgrastim) with a risk of Capillary Leak Syndrome

On 10 April 2014, Amgen Canada Inc., in consultation with Health Canada, informed healthcare professionals of important new safety information concerning the risk of Capillary Leak Syndrome (CLS) associated with the granulocyte colony stimulating factors (G-CSF) Neupogen® and Neulasta®. Cases of CLS have been reported in patients undergoing chemotherapy who were receiving Neupogen® or Neulasta®, and donors undergoing peripheral blood progenitor cell mobilization who were receiving Neupogen®. CLS can cause circulatory shock and may be fatal. It is associated with hypotension, generalized edema, hypoalbuminemia and hemoconcentration. Episodes can vary in frequency and severity. Should symptoms of CLS be suspected, administration of Neupogen® or Neulasta® needs to be stopped and the patient closely monitored. The Neupogen® or Neulasta® Product Monographs in Canada were being updated to reflect this new safety information.

In Hong Kong, there are 11 and 1 registered pharmaceutical products containing filgrastim and pegfilgrastim respectively. They are prescription only medicines. DH had not received any adverse drug reactions related to the products. In view of Health Canada's announcement, a letter to healthcare professionals to draw their attention and urge them to report any ADR related to the drug was issued on 11 April 2014, and the matter will be discussed in the meeting of Registration Committee.

European Union (EU): PRAC recommends against combined use of medicines affecting the renin-angiotensin (RAS) system

On 11 April 2014, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) had reviewed the risks of combining different classes of medicines that act on the renin-angiotensin (RAS) system, a hormone system that controls blood pressure and the volume of fluids in the body. These medicines (called RAS-acting agents) belong to three main classes: angiotensin-receptor blockers (ARBs, sometimes known as sartans), angiotensin-converting enzyme inhibitors (ACE-inhibitors) and direct renin inhibitors such as aliskiren.

The PRAC had advised that combining medicines from any two of these classes should not be recommended, and in particular that patients with diabetic nephropathy should not be given an ARB with an ACE-inhibitor. Where such combination (dual blockade) is considered absolutely necessary, it must be carried out under specialist supervision with close monitoring of kidney function, fluid and salt balance and blood pressure. The combination of aliskiren with an ARB or ACE-inhibitor is strictly contraindicated in those with kidney impairment or diabetes.

The PRAC recommendation would be forwarded to the Committee for Medicinal Products for Human Use (CHMP) which would adopt the EMA's final opinion.

The PRAC also found evidence from several large studies in patients with various pre-existing heart and circulatory disorders, or with type 2 diabetes, that combination of an ARB with an ACE-inhibitor was associated with an increased risk of hyperkalaemia, kidney damage or low blood pressure compared with using either medicine alone. Further details of the review and the evidence behind it, as well as recommendations for patients and healthcare professionals, will be made available at the time of the CHMP opinion.

In Hong Kong, registered pharmaceutical products containing medicine affecting the RAS system (i.e. ARBs, ACE-inhibitors, and direct renin inhibitors) are prescription only medicines. Safety alerts regarding the combination of aliskiren with ACE-inhibitors, or ARBs had been reported in Drug News Issues No. 26 and 28. The matter was discussed by the Registration Committee of the Pharmacy and Poisons Board in August 2012, and decided that the sales pack labels and/or package

inserts of products containing aliskiren should include the appropriate safety information as stated in Drug News Issue No. 28. DH will remian vigilant on any safety updates of the drugs and actions taken by overseas regulatory authorities of any action deemed necessary.

EU: Start of review of codeine-containing medicines when used for cough and cold in children

On 11 April 2014, the EMA had started a review of codeine-containing medicines when used for cough and cold in children (aged below 18 years). This followed a previous review of these medicines when used for pain relief in children, which was triggered by concerns over the risk of morphine toxicity.

Following the previous review, several measures were introduced in order to minimise the risk of morphine toxicity when using codeine for pain relief. These included a recommendation that children with conditions associated with breathing problems should not use codeine. As the reasons for this recommendation may also apply to the use of codeine for cough and cold in children, the German medicines agency (BfArM) has now requested an EU-wide review of such use. The EMA would evaluate the available evidence on the benefit-risk balance of codeine-containing medicines when these medicines are used for cough and cold in children.

In Hong Kong, there are 354 registered oral pharmaceutical products containing codeine, which is an ingredient used to relieve pain, as well as cough and cold. Related news regarding the use of codeine have also been reported in Drug News Issues No. 12, 34, 40 and 44. The matter had been discussed in the meeting of the Registration Committee of the Pharmacy and Poisons Board, and decided that codeine is not recommended for use in children less than 12 years of age, and the sales pack and package insert should be updated to include the appropriate safety information as outlined in Drug News Issue No. 44. DH will remain vigilant on any safety updates of the drug and actions taken by overseas regulatory authorities of any action deemed necessary.

United States (US): Epidural Corticosteroid Injection - risk of rare but serious neurologic problems

On 23 April 2014, the US Food and Drug Administration (FDA) is warning that injection of corticosteroids into the epidural space of the spine may result in rare but serious adverse events, including loss of vision, stroke, paralysis, and death. The injections are given to treat neck and back pain, and radiating pain in the arms and legs. FDA is requiring the addition of a Warning to the drug labels of injectable corticosteroids to describe these risks.

Injectable corticosteroids are commonly used to reduce swelling or inflammation. Injecting corticosteroids into the epidural space of the spine has been a widespread practice for many decades; however, the effectiveness and safety of epidural administration of corticosteroids have not been established, and FDA has not approved corticosteroids for this use.

FDA started investigating this safety issue when FDA became aware of medical professionals' concerns about epidural corticosteroid injections and the risk of serious neurologic adverse events. To raise awareness of the risks of epidural corticosteroid injections in the medical community, FDA's Safe Use Initiative convened a panel of experts, including pain management experts to help define the techniques for such injections which would reduce preventable harm. The expert panel's recommendations would be released when they are finalized. FDA would convene an Advisory Committee meeting of external experts in late 2014 to discuss the benefits and risks of epidural corticosteroid injections and to determine if further FDA actions are needed.

In Hong Kong, there are 25 registered injectable products containing corticosteroids such as methylprednisolone, hydrocortisone, triamcinolone, betamethasone and dexamethasone. All are prescription only medicines. DH had not received any adverse reaction report in relation to epidural injection of the drugs, and will keep vigilant on any safety updates of the drugs. In view of the FDA's announcement, a letter to healthcare professionals to draw their attention was issued on 24 April 2014, and the matter will be discussed in the meeting of the Registration Committee.

Singapore: New contraindication on the use of high-dose diclofenac for more than four weeks in selected groups of patients

On 25 April 2014, HSA informed healthcare professionals that the use of high-dose systemic diclofenac (150mg/day) for more than four weeks is contraindicated in patients with established cardiovascular (CV) disease or uncontrolled hypertension. This regulatory decision was made following HSA's benefit-risk assessment, in consultation with its Product Vigilance Advisory Committee (PVAC) and several other clinical experts. The safety review was conducted in response to a growing body of scientific evidence suggesting that high doses of diclofenac used over a long duration is associated with increased CV risks. In addition to the new contraindication, healthcare professionals are advised that if systemic diclofenac treatment is needed, patients with established CV disease, uncontrolled hypertension or significant CV risk factors (e.g., hypertension, hyperlipidaemia, diabetes mellitus and smoking) should be treated only after careful consideration and at doses ≤100mg daily if the treatment is for more than 4 weeks. As the CV risks of diclofenac may increase with dose and duration of exposure, diclofenac should always be prescribed at the lowest effective daily dose and for the shortest duration possible. Healthcare professionals are encouraged to take into consideration the above recommendations when prescribing diclofenac.

In Hong Kong, there are 162 registered pharmaceutical products containing diclofenac indicated for systemic use (given by means such as capsules, tablets or injections) and are prescription only medicines. Safety alerts regarding diclofenac and other non-steroidal anti-inflammatory drugs associated with cardiovascular risks had been released by MHRA, EMA and HSA, and were reported in Drug News Issues No. 24, 36, 43 and 53. Letters to inform healthcare professionals were issued on 30 September 2011 and 3 March 2014. As stated in Drug News Issue No. 53, the matter had been discussed in the meeting of the Registration Committee in the meeting of May 2014. The Committee has decided that the innovator company shall provide details of the situation in Singapore and relevant scientific data. DH will remain vigilant on new announcements by other overseas health authorities and will follow-up the reply from the innovator company.

Singapore: Risk of Intraocular Floppy Iris Syndrome (IFIS) with risperidone or paliperidone in patients undergoing cataract surgery

On 25 April 2014, HSA alerted healthcare professionals to the risk of intraoperative floppy iris syndrome (IFIS) observed during cataract surgery in patients treated with risperidone or paliperidone. IFIS has been observed during cataract surgery in patients on alpha-adrenergic antagonists and there exists a possible biological plausibility of an association between risperidone and IFIS, although such cases are very rare. The association is also extended to paliperidone since it is the active metabolite of risperidone and therefore shares similar pharmacological and safety profiles. A Dear Healthcare Professional Letter was issued to inform psychiatrists and opthalmologists of this emerging risk. The letter included advisories such as recommending cataract surgeons to ask their patient about current or prior use of risperidone or paliperidone when taking the medication history of their patients preoperatively, and to approach the surgery with caution when IFIS is suspected. Healthcare professionals are advised to document the use of α1-adrenergic antagonists, including risperidone and paliperidone, when making a patient referral for cataract surgery.

In Hong Kong, there are 73 registered pharmaceutical products containing risperidone and 8 containing paliperidone. All of them are prescription only medicines indicated for the treatment of schizophrenia. Related news has been released by Health Canada and was reported in Drug News Issue No. 49. The Registration Committee had already discussed the issue in February 2014, and decided that the sales pack labels and/or package inserts of pharmaceutical products containing risperidone or paliperidone should include the following new safety information:

Intraoperative Floppy Iris Syndrome (IFIS) has been observed during cataract surgery in patients treated with medicines with alpha1a-adrenergic antagonist effect, such as (Product Name).

Safety Update

IFIS may increase the risk of eye complications during and after the operation. Current or past use of medicines with alpha1a-adrenergic antagonist effect should be made known to the ophthalmic surgeon in advance of surgery. The potential benefit of stopping alpha1 blocking therapy prior to cataract surgery has not been established and must be weighed against the risk of stopping the antipsychotic therapy.

Singapore: Minocycline and risk of benign intracranial hypertension

On 25 April 2014, HSA had reviewed the safety profile of minocycline in relation to the risk of benign intracranial hypertension. Benign intracranial hypertension (also known as pseudotumour cerebri) involves a persistent rise in cerebrospinal fluid pressure and is characterised by headache, nausea, vomiting and vision disturbances, including papilloedema with occasional sixth-nerve palsy. While rare, benign intracranial hypertension is known to be associated with tetracyclines, and in particular, with minocycline treatment. Concomitant use of isotretinoin (or other systemic retinoids) with minocycline should be avoided because isotretinoin is also known to be associated with benign intracranial hypertension. Healthcare professionals are recommended to consider the possibility of benign intracranial hypertension in patients treated with minocycline, if signs and symptoms consistent with this diagnosis are identified.

In Hong Kong, there are 7 registered pharmaceutical products containing an antimicrobial minocycline, and all of them are prescription only medicines. In view of the findings by HSA, a letter to inform healthcare professionals to draw their attention was issued on 28 April 2014, and the matter will be discussed in the meeting of the Registration Committee.

Drug Recall

Recall of Premier Topicale Topical Anesthetic Gel

On 30 April 2014, DH instructed a licensed drug wholesaler, 3 On Dental & Industrial Supplies Co, Ltd. (3 On), to recall from the market all flavours of Premier Topicale Topical Anesthetic Gel as they are unregistered pharmaceutical products in Hong Kong.

Upon the DH's investigation into a public complaint, the premises of 3 On were raided today and different flavours of the above product were seized. Hong Kong pharmaceutical product registration numbers were not found on the product labels. Preliminary investigation revealed that the products were imported into Hong Kong by 3 On and had been supplied to local dentists.

The above product, labelled as containing 18 per cent benzocaine, is used as a local anesthetic to be applied on the oral mucosa. Side-effects include dizziness, blurred vision, nausea and vomiting. They can only be sold in pharmacies under the supervision of registered pharmacists.

As on 30 April 2014, DH had not received any adverse drug reaction reports in connection with the product and DH had closely monitored the recall. A notice was released on the Drug Office's website on the same day to alert the public of the recall. In addition, DH had informed local dentists and relevant professional bodies to advise them not to use the products concerned because unregistered pharmaceutical products have not been evaluated by the Board and their safety, quality and efficacy may not be guaranteed.

Public urged not to buy or use unregistered pharmaceutical products

On 1 April 2014, DH appealed to members of the public not to buy or use unregistered pharmaceutical products as they may contain Western drug ingredients that might be dangerous to health.

During the DH's market surveillance, samples of an oral product (without English name) were purchased from a hawker store in Yau Ma Tei for analysis. Results from the Government Laboratory confirmed that the samples contained sildenafil, a Part I poison.

The hawker store was raided on 31 March 2014 by the DH and the Police. Apart from the oral product, two other unregistered products, namely Lido spray and Procomil spray, both labelled as containing lignocaine (another Part I poison), were also found during the operation. Although the spray products were labelled with "HK-24862" and "HK-22498" respectively, these numbers are not valid pharmaceutical product registration numbers. The oral product did not bear any registration number on the label. A 52-year-old woman was arrested for illegal sale and possession of unregistered pharmaceutical products and Part I poisons.

Products containing sildenafil are prescription drugs for the treatment of erectile dysfunction and should only be supplied at pharmacies under the supervision of a registered pharmacist upon a doctor's prescription. Side effects of sildenafil include low blood pressure, headache, vomiting, dizziness and transient vision disturbances. It may interact with some drugs (such as nitroglycerin for the treatment of angina) and cause a decrease in blood pressure to dangerous levels. Improper use of sildenafil may pose serious health risks, especially for patients with heart problems.

Lignocaine is a local anaesthetic for the relief of pain or for desensitisation of the skin before minor operations. It may cause side effects such as hypersensitive reactions.

Woman arrested for suspected illegal sale of slimming product with undeclared and banned drug substances

On 3 April 2014, a joint operation was conducted by DH and the Police resulting in the arrest of a 43-year-old woman for the illegal sale of a slimming product named Slimup Extra, which is suspected to contain undeclared and banned drug substances.

Acting on intelligence, DH found that the above slimming product was offered for sale through a mobile phone communication application. A sample was purchased for analysis and the test results from the Government Laboratory revealed that the product contains two undeclared and banned Western medicines, namely sibutramine and phenolphthalein. During the operation, the seller was arrested by the Police for suspected illegal sale and possession of a Part I poison and an unregistered pharmaceutical product.

Sibutramine is a Part I poison and was once used as an appetite suppressant. Since November 2010, products containing sibutramine have been banned in Hong Kong because of an increased cardiovascular risk. Phenolphthalein was once used for treating constipation, but has been banned for its possible cancer-causing effect.

Members of the public are strongly urged not to buy or consume products of unknown or doubtful composition. 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.

Public urged not to buy or consume slimming product with undeclared and banned Western drug ingredients

On 4 April 2014, DH appealed to members of the public not to buy or consume a slimming product called Yanhee Slim as it is suspected to contain undeclared and banned drug ingredients that might be dangerous to health.

During the DH's market surveillance, a sample of the above slimming product was purchased through a mobile communication application for analysis. Test results from the Government Laboratory revealed that the product contains sibutramine.

Sibutramine is a Part I poison and was once used as an appetite suppressant. Since November 2010, products containing sibutramine have been banned in Hong Kong because of an increased cardiovascular risk.

Drug Incident

Members of the public are strongly urged not to buy or consume products of unknown or doubtful composition. 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.

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,
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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.