Drug News
藥 物 情 報

Issue Number 72

This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in October 2015 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: Azithromycin and drug reaction with eosinophilia and systemic symptoms (DRESS)

On 8 October 2015, Singapore Health Sciences Authority (HSA) highlighted to healthcare professionals that overseas cases of drug reaction with eosinophilia and systemic symptoms (DRESS) associated with the use of azithromycin.

DRESS is a severe drug reaction characterised by rash, fever, lymphadenopathy, and single or multiple organ involvement (e.g., liver, kidney) that typically occurs within eight weeks of drug initiation. Haematologic abnormalities, including eosinophilia and atypical lymphocytosis, are also key characteristics of this syndrome.

In April 2014, Health Canada highlighted in its Canadian Adverse Reaction Newsletter that the package inserts (PI) for azithromycin-containing products have been updated with information on DRESS following the receipt of a domestic report of DRESS.

HSA has not received any reports of DRESS associated with the use of azithromycin. The company has initiated a labelling update for the Zithromax® range of products in Singapore to warn of reports of DRESS.

Healthcare professionals are encouraged to be vigilant to the signs and symptoms of DRESS in patients who are prescribed azithromycin. These may include rash, fever, lymphadenopathy, haematological abnormalities and multiorgan involvement. Early and prompt discontinuation of the offending drug is important to achieve the best outcome in patients with DRESS.

In Hong Kong, there are 70 registered pharmaceutical products containing azithromycin, and are prescription only medicines. As on 3 November 2015, the Department of Health (DH) has received one case of adverse drug reaction (ADR) on azithromycin, and it was not related to DRESS. In view of Singapore HSA's announcement, the DH issued a letter to inform local healthcare professionals of the risk was issued on 8 October 2015. The matter will be discussed in the Registration Committee of the Pharmacy and Poisons Board.

Singapore: Testosterone and risk of cardiovascular events

On 8 October 2015, Singapore HSA announced on the website that healthcare professionals has been informed of the overseas signals of cardiovascular (CV) events associated with the use of testosterone-containing products. Safety reviews conducted by international regulatory agencies have concluded that the signal of CV risk remains weak and further investigations by the manufacturers, such as the conduct of a well-designed clinical trial and close monitoring of these safety events, are necessary to confirm this risk.

Testosterone is a steroid hormone that plays a role in the development of androgenic and anabolic processes. It is mainly indicated for replacement therapy in males with primary and secondary hypogonadal disorders. Some of the testosterone-containing products are also indicated for

osteoporosis caused by androgen deficiency, or for masculinisation in female to male transsexuals. Testosterone was first licensed in Singapore in 1990, and there are currently seven testosterone-containing products in different dosage forms, ranging from oral capsules to subcutaneous implants.

Reviews on the CV risk of testosterone have been conducted by the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), Health Canada and New Zealand Medsafe.

HSA has also consulted local experts (urologists and cardiologists) regarding the signal of CV risk with testosterone. Some of the experts were of the opinion that methodological limitations and biases may have impacted the findings of the observational studies mentioned in overseas reviews. HSA is working with the companies to ensure that the warnings and precautions relating to CV events are adequately highlighted across the package insert (PI) of testosterone-containing products.

In Hong Kong, there are eight registered pharmaceutical products containing testosterone or methyltestosterone, and are prescription only medicines. The DH noted that US FDA, Health Canada and the EMA have started to review the risk of cardiovascular events of testosterone products, and the related news was posted on the Drug News Issues No. 52, 56, 57, 60 and 65. The DH issued letters to inform local healthcare professionals on the above safety warnings on 16 July 2014 and 13 October 2014. As on 3 November 2015, the DH has received one case of ADR on testosterone, and it was not related to cardiovascular complications. The matter was discussed by the Registration Committee of the Pharmacy and Poisons Board on 17 February 2015. The Committee decided that the sales pack labels and/or package inserts should be updated to include the relevant safety information:

1. Testosterone replacement therapy should only be given to men when deficiency of the hormone has been confirmed by clinical features and biochemical tests. Testosterone levels should then be monitored regularly during treatment. Haemoglobin, haematocrit, liver function and blood lipid profile should also be monitored regularly.

2. In patients suffering from severe cardiac, hepatic, or renal insufficiency or ischaemic heart disease, treatment with testosterone may cause severe complications characterised by oedema with or without congestive cardiac failure. In such a case, treatment must be stopped immediately.

3. Caution is advised in patients with pre-existing hypertension, since testosterone may cause an increase in blood pressure.

4. There is limited experience on the safety and efficacy of the use of these medicines in patients over 65 years of age. It should be borne in mind that physiological testosterone levels naturally decrease somewhat with age.

5. Venous Thromboembolism
There have been postmarketing reports of venous thromboembolic events, including deep vein thrombosis (DVT) and pulmonary embolism (PE), in patients using testosterone products such as [Product Name]. Evaluate patients who report symptoms of pain, edema, warmth and erythema in the lower extremity for DVT and those who present with acute shortness of breath for PE. If a venous thromboembolic event is suspected, discontinue treatment with [Product Name] and initiate appropriate workup and management.

EU: Review of Tysabri started

On 12 October 2015, EMA announced on the website that a review of the multiple sclerosis medicine Tysabri (natalizumab) has been started. The aim of the review is to assess whether the advice given to healthcare professionals and patients on how to manage the known risk of progressive multifocal leukoencephalopathy (PML) with this medicine should be revised in the light of new scientific evidence.

PML is a rare brain infection caused by John Cunningham virus (JCV), which has symptoms that may be similar to those of a multiple sclerosis attack, and may result in severe disability or death. It is already known that the risk of PML increases the longer a patient has been receiving Tysabri, especially in patients treated for more than two

years. The risk of PML is also higher if the patient used immunosuppressant medicines before starting Tysabri, or if the patient has tested positive for antibodies against the virus that causes PML.

Scientific evidence on PML is rapidly growing. New data seem to indicate that the methods used to calculate the risk of PML may need to be revised and that testing for PML in patients with no symptoms may need to be performed more frequently than currently recommended. New diagnostic tests have recently been developed and there is a need to assess whether this has an impact on the current prescribing advice.

The EMA will now evaluate the available data on the risk of PML with Tysabri with the aim of better defining the risk of PML and identifying further measures to minimise it, and will issue an opinion on whether changes to the marketing authorisation are needed.

In Hong Kong, there is one registered pharmaceutical product containing natalizumab, namely Tysabri Concentrate for Solution for Infusion 300mg (HK-61519). It is registered by UCB Pharma (Hong Kong) Limited, and is a prescription only medicine. As on 3 November 2015, the DH has not received any ADR case on natalizumab. The local package insert of the product has already included the warning on PML. As the EMA has just started the review of natalizumab, and will issue an opinion on whether changes to the marketing authorisation are needed when the review is completed, the DH will remain vigilant on the review's result and safety updates from other overseas drug regulatory authorities.

UK: Mirabegron (Betmiga): risk of severe hypertension and associated cerebrovascular and cardiac events

On 14 October 2015, the UK Medicines and Healthcare products Regulatory Agency (MHRA) announced that Mirabegron was now contraindicated in patients with severe uncontrolled hypertension; advice about regular monitoring is being introduced because of cases of severe hypertension.

Mirabegron (Betmiga) is a beta 3-adrenoceptor agonist used in the management of urinary frequency, urgency, and incontinence in overactive bladder syndrome.

An EU-wide review of the latest safety data for mirabegron has led to new measures to help reduce the risks of severe hypertension. It is already known that mirabegron can increase blood pressure. However, cases of severe hypertension have been reported, which include hypertensive crisis associated with reports of cerebrovascular and cardiac events (mainly transient ischaemia attack or stroke) - some with a clear temporal relation to mirabegron use.

Mirabegron is now contraindicated in patients with severe uncontrolled hypertension (systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥110 mm Hg, or both). Regular monitoring of blood pressure is important, especially in patients with pre-existing hypertension. Data are limited regarding use of mirabegron in patients with stage 2 hypertension (ie, systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg) and it should therefore be used with caution in this group.

As for some other patient subgroups, Mirabegron is not recommended in patients with severe renal impairment (ie, GFR 15–29 mL/min/1.73 m2) or in those with moderate hepatic impairment (ie, Child-Pugh Class B) who are also taking strong inhibitors of cytochrome P450 3A such as itraconazole, ketoconazole, ritonavir, or clarithromycin. The dose of mirabegron in patients with mild to moderate renal impairment (ie, GFR 30–89 mL/min/1.73 m2) or those with mild hepatic impairment (ie, Child-Pugh Class A) who are also taking strong inhibitors of cytochrome P450 3A should be reduced to 25 mg once daily.

Healthcare professionals are advised of the following key safety updates:

- Mirabegron is contraindicated in patients with severe uncontrolled hypertension (systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥110 mm Hg, or both), and
- Blood pressure should be measured before starting treatment and monitored regularly during treatment, especially in patients with hypertension.

In Hong Kong, there are two registered pharmaceutical products containing mirabegron, namely Betmiga Prolonged-release Tab 25mg (HK-62460) and 50mg (HK-62461). Both products are prescription only medicines registered by Astellas Pharma Hong Kong Company Limited. As on 3 November 2015, the DH has not received any ADR case on mirabegron. In view of the MHRA's announcement, the DH issued a letter to inform local healthcare professionals of the risk on 15 October 2015, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

US: Hepatitis C Treatments Viekira Pak and Technivie - Risk of serious liver injury

FDA was warning that hepatitis C treatments Viekira Pak and Technivie can cause serious liver injury mostly in patients with underlying advanced liver disease on 22 October 2015, and requiring the manufacturer to include information about serious liver injury adverse events to the Contraindications, Warnings and Precautions, Postmarketing Experience, and Hepatic Impairment sections of the Viekira Pak and Technivie drug labels.

Viekira Pak and Technivie are used to treat chronic hepatitis C. Viekira Pak is a fixed-dose combination of dasabuvir, ombitasvir, paritaprevir, and ritonavir used with or without ribavirin, another hepatitis C medicine. Technivie is a fixed-dose combination of ombitasvir, paritaprevir, and ritonavir, used in combination with ribavirin.

FDA review of adverse events reported to the FDA Adverse Event Reporting System (FAERS) database and to the manufacturer of these medicines, AbbVie, identified cases of hepatic decompensation and liver failure in patients with underlying liver cirrhosis who were taking these medicines. Some of these events resulted in liver transplantation or death. These serious outcomes were reported mostly in patients taking Viekira Pak who had evidence of advanced cirrhosis even before starting treatment with it.

Since the approvals of Viekira Pak in December 2014 and Technivie in July 2015 in the US, at least 26 worldwide cases submitted to FAERS were considered to be possibly or probably related to Viekira Pak or Technivie. In most of the cases, liver injury occurred within 1 to 4 weeks of starting treatment. Some of the cases occurred in patients for whom these medicines were contraindicated or not recommended. FAERS includes only reports submitted to FDA, so there are likely additional cases about which FDA is unaware.

Healthcare professionals should closely monitor for signs and symptoms of worsening liver disease, such as ascites, hepatic encephalopathy, variceal hemorrhage, and/or increases in direct bilirubin in the blood.

In Hong Kong, Viekira Pak Tablets (HK-63695) is a pharmaceutical product registered by Abbvie Limited (Abbvie), and is a prescription only medicine; while Technivie is not registered. As on 3 November 2015, the DH has received four cases of ADRs after taking Viekira Pak, and none of them was related to liver injury. As confirmed with Abbvie, the company is going to apply for update of package insert of the product to include the relevant information. In view of the US FDA's announcement, the DH issued a letter to inform local healthcare professionals of the warning on 23 October 2015. The matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

US: Kayexalate (sodium polystyrene sulfonate) - FDA requires drug interaction studies

On 22 October 2015, FDA was requiring the Kayexalate manufacturer to conduct studies to investigate Kayexalate's potential to bind to other medications administered by mouth – drug interactions that could affect how well the other medications work.

Kayexalate (sodium polystyrene sulfonate) and generic brands Kionex and SPS are used to treat hyperkalemia, a serious condition in which the amount of potassium in the blood is too high. They work by binding potassium in the large intestine so it can be removed from the body.

The approved labeling for Kayexalate in the US describes its potential to decrease absorption of lithium and thyroxine; however, extensive drug-drug interaction studies with Kayexalate have not been performed. During FDA’s review of another

potassium-lowering drug, Veltassa (patiromer), FDA found that Veltassa bound to about half of the medications tested, some of which are commonly used in patients who require potassium-lowering drugs. Such binding could decrease the effects of these medications. The label for Veltassa contains a warning not to take other orally administered medications within 6 hours of taking Veltassa.

Similar to Veltassa, Kayexalate may also bind to other medications administered by mouth. To reduce this potential risk, prescribers and patients should consider separating Kayexalate dosing from other medications taken by mouth by at least 6 hours. This includes both prescription medications, such as antibiotics, blood pressure lowering agents and blood thinners, and those purchased over-the-counter without a prescription, such as antacids and laxatives. Healthcare professionals should monitor blood levels or clinical response to the other medications when appropriate.

If the studies conducted by the Kayexalate manufacturer, Concordia Pharmaceuticals, confirm significant interactions with other medications, FDA will require all manufacturers of sodium polystyrene sulfonate products to update the drug labels to include information about these drug interactions.

Prescribers and patients should consider separating Kayexalate dosing from other medications taken by mouth by at least 6 hours. Healthcare professionals should monitor blood levels or clinical response to the other medications when appropriate. Patients should not stop taking their potassium-lowering drugs without talking to their healthcare professional.

In Hong Kong, there are two registered pharmaceutical product containing sodium polystyrene sulfonate, namely Resonium A Powder (HK-42418) and PMS-Sodium Polystyrene Sulfonate Powder (HK-44860); while there is no registered pharmaceutical product containing patiromer. In view of the possible drug interaction between sodium polystyrene sulfonate and other drugs, the DH issued a letter to inform local healthcare professionals of the risk on 23 October 2015. As the US FDA is requiring the brand product's manufacturer to conduct studies to confirm whether there will be significant drug interaction, and labels will be updated if the result is affirmative, the DH will remain vigilant on the US FDA's conclusion and safety updates by other overseas drug regulatory authorities for consideration of any action deemed necessary.

Canada: Strontium health products: New restrictions to address possible heart and circulatory-related risks

At Health Canada's request on 22 October 2015, companies are strengthening product labels for certain strontium-containing natural health products with new restrictions, to minimize a possible increased risk of cardiovascular-related side effects (e.g., heart attack, stroke, blood clots) in people who are at risk of these types of events.

The label changes apply to strontium-containing products with a daily dose between 4 mg and 682 mg, which are used to help support bone mineral density. These products currently contain either strontium citrate, strontium gluconate or strontium lactate.

The new directions limit these products to users who have no history of, or risk factors for, heart disease, circulatory problems or blood clots. As well, consumers are advised to consult a healthcare practitioner for use longer than 6 months.

The review was undertaken in light of findings in Europe that led to restrictions for use of oral prescription drugs containing strontium at 680 mg/ day (as strontium ranelate), due to the increased risk of cardiovascular events seen in patients who have risk factors for heart or circulatory-related side effects.

The Health Canada review found that there is no information available on the cardiovascular risk with strontium ranelate at levels lower than 680 mg/day, or with non-ranelate forms of strontium at any dose. No Canadian or international reports of cardiovascular side effects involving non-ranelate strontium products were identified at the time of the review. The review also found there is not enough information to compare how strontium

ranelate is absorbed in the body relative to other, non-ranelate forms of strontium.

While uncertainties remain, Health Canada is using a precautionary approach and considers that strontium, regardless of the form it comes in or dose taken, may have a potential risk of cardiovascular side effects in people who are already at risk.

Health Canada continues to consider whether additional risk minimization measures may be needed to further restrict the use of strontium-containing products, particularly those products with higher daily doses. Measures under consideration include further changes to the directions for use or changing how certain strontium-containing products (e.g. with higher doses) are regulated so that they are available by prescription only, under the supervision of a healthcare professional.

In Hong Kong, there is one registered pharmaceutical product containing strontium ranelate, namely Protos Granules for Oral Suspension 2g (HK-53835), and is a prescription only medicine registered by Servier Hong Kong Ltd. Safety alerts regarding risk of cardiovascular and cerebrovascular events associated with strontium had been issued by the EMA and the TGA and were reported on the Drug News Issues No. 25, 42 and 54. The DH issued letters to inform local healthcare professional of the risk on 19 March 2012 and 15 April 2013. As on 3 November 2015, the DH has not received any ADR case on strontium. The matter was discussed by the Registration Committee of the Pharmacy and Poisons Board (the Committee) in September 2013, February 2014, and May 2014. For the discussions of Februray and May 2014, the Committee decided that the sales pack labels and/or package inserts should be updated to include the relevant safety information IN CAPITAL, on top of the September 2013:

"Indications"
- Treatment of severe osteoporosis:
- in postmenopausal women,
- IN ADULT MEN,
at high risk for fracture, FOR WHOM TREATMENT WITH OTHER MEDICINAL PRODUCTS APPROVED FOR THE TREATMENT OF OSTEOPOROSIS IS NOT POSSIBLE DUE TO, FOR EXAMPLE, CONTRAINDICATIONS OR INTOLERNACE.
In postmenopausal women, strontium ranelate reduces the risk of vertebral and hip fractures

- The decision to prescribe strontium ranelate should be based on an assessment of the individual patient's overall risks

"Contraindications"
- Established, current or past history of ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

- Uncontrolled hypertension.
"Posology"
- Treatment should only be initiated by a physician with experience in the treatment of osteoporosis.

"Special warnings and precautions for use"
- In pooled randomized placebo-controlled studies of post-menopausal osteoporotic patients, a significant increase in myocardial infarction has been observed in [brand name] treated patients compared to placebo.

- Before starting treatment and at regular intervals (GENERALLY EVERY 6 TO 12 MONTHS), patients should be evaluated with respect to cardiovascular risk.

- Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with strontium ranelate after careful consideration.

- Treatment should be stopped if the patient develops ischaemic heart disease, peripheral arterial disease, cerebrovascular disease or if hypertension is uncontrolled"

EU: EMA recommends additional measures to prevent use of mycophenolate in pregnancy

On 22 October 2015, the EMA has warned that the transplant medicine mycophenolate (authorised

centrally as CellCept and nationally under various names) must not be used in pregnancy unless no suitable alternative is available to prevent transplant rejection. This follows a routine re-assessment of the benefits and safety of these medicines, which provided updated evidence on the risk of birth defects and spontaneous abortions when pregnant women were exposed to the medicine.

Mycophenolate (mycophenolate mofetil or mycophenolic acid) is an immunosuppressant (a medicine that suppresses the action of the immune system, the body's natural defences). It is approved for use with other medicines to prevent rejection of the transplanted organ in patients given a kidney, heart or liver transplant. In the EU, mycophenolate mofetil has been authorised centrally as CellCept and other names since 1996, and mycophenolate has also been authorised through various national procedures.

Although the product information for these medicines already contains warnings against use in pregnancy, these will now be significantly strengthened by the addition of new contraindications, advice and information. Updated product information will emphasise that women and men using the medicine should use effective contraception and that pregnancy tests should be used before and during treatment as needed to rule out unintended pregnancy. In addition, doctors should properly explain the risks to patients and their partners, and educational material will be produced for patients and healthcare professionals to assist with this.

EMA's recommendations are based on the assessment of updated evidence on the teratogenic risks.

- A cumulative review found that around 45 to 49% of pregnancies in women exposed to mycophenolate resulted in spontaneous abortion, compared with reported frequencies of 12 to 33% in solid organ transplant patients treated with other immunosuppressants.
- The reported incidence of malformation in the offspring of mothers exposed to mycophenolate during pregnancy is 23 to 27% compared with 4 to 5% in transplant patients treated with other immunosuppressants, and 2 to 3% in the overall population. Malformations associated with mycophenolate have included abnormalities of the ear, eye and face, congenital heart disease including septal defects, polydactyly or syndactyly, tracheo-oesophageal malformations such as oesophageal atresia, effects on the nervous system such as spina bifida, and renal abnormalities.

In Hong Kong, there are 17 registered pharmaceutical products containing mycophenolate mofetil or mycophenolic acid. All products are prescription only medicines. As on 3 November 2015, the DH has received four cases of ADRs on the drug, and one of them was related to missed abortion after taking the drug. In view of the EMA's announcement, the DH issued a letter to inform local healthcare professionals of the risk on 26 October 2015. The matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board. The DH will remain vigilant on any safety updates of the drug by other overseas drug regulatory authorities.

US: Entacapone - FDA review found no increased cardiovascular risks

An FDA safety review has found no clear evidence of an increased risk of heart attacks, stroke, or other cardiovascular events associated with the use of entacapone for the treatment of Parkinson's disease. As a result, recommendations announced by FDA on 26 October 2015 for using Comtan (entacapone) and Stalevo (a combination of entacapone, carbidopa, and levodopa) will remain the same in the drug labels.

FDA alerted patients and healthcare professionals about a possible increased risk for cardiovascular events and death with Stalevo in August 2010. This possible safety issue was observed in a clinical trial called the Stalevo Reduction in Dyskinesia Evaluation in Parkinson's Disease (STRIDE-PD) and in a meta-analysis that combined the cardiovascular-related findings from 15 clinical trials comparing Stalevo to carbidopa/levodopa. Carbidopa and levodopa have been used extensively and have not been shown to have an increased cardiovascular risk. FDA was concerned that the entacapone in Stalevo was responsible for these

cardiovascular risks because the comparison drugs do not contain this ingredient.

To better understand the significance of these findings, FDA required the Stalevo manufacturer, Novartis, to study the potential for cardiovascular risk with the entacapone component of the drug. FDA examined the results from this required study and from one additional study and concluded they do not show an increased risk of cardiovascular adverse events with entacapone. The results observed in the original meta-analysis were driven by results of a single study (STRIDE-PD), which was not designed to assess cardiovascular risks. FDA believes that the meta-analysis and STRIDE-PD results are chance findings and do not represent a true increase in risk due to entacapone. Entacapone-containing products, Comtan and Stalevo, have been shown to be effective in treating symptoms of Parkinson's disease, such as muscle stiffness, tremors, spasms, and poor muscle control. The combination of entacapone with carbidopa and levodopa in Stalevo has been shown to reduce end-of-dose "wearing-off" in patients with Parkinson's disease to a greater degree than with entacapone alone or with the two-drug combination of carbidopa and levodopa.

In Hong Kong, there are eight registered pharmaceutical products containing entacapone under the brand names of Comtan (contains entacapone) and Stalevo (contains entacapone, levodopa and carbidopa) which are registered by Novartis Pharmaceuticals (HK) Limited, and Entacapone-Teva (contains entacapone) which is registered by The International Medical Company Limited. All products are prescription only medicines. As on 3 November 2015, the DH has not received any ADR case on entacapone-containing products. In view of the conclusion of the US FDA that no increased cardiovascular risks was found associated with the use of entacapone, the DH issued a letter to inform local healthcare professionals of the update on 27 October 2015. The DH will remain vigilant on any safety update of the drug.

Taiwan: Risk communication on drug containing febuxostat

It was noted from Taiwan FDA website on 28 October 2015 that it has published a few adverse drug reactions received in recent years in connection with the use of febuxostat such as suspected Stevens-Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS), of which there was a death case reported. These cases are mainly involved in the elderly or chronic renal failure patients, although some adverse effects associated with skin maybe due to other drugs taken, the correlation of such adverse effect with the product containing febuxostat still cannot be ruled out.

The Taiwan FDA has stated:
The Chinese version of product insert of the approved product containing febuxostat (Feburic) has included the adverse effects such as "generalized rash, Stevens-Johnson syndrome, allergic skin reactions," under the category of "Postmarketing experience".The details of the requirement are at the following website:
http://www.fda.gov.tw/TC/siteList.aspx?sid=1571

In Hong Kong, there are two registered pharmaceutical products containing febuxostat, namely Feburic Tablets 80mg (HK-61185) and 120mg (HK-61186) which are registered by Astellas Pharma Hong Kong Company Limited, and are prescription only medicine. The package inserts of those products have already included the relevant warning on serious skin allergic reaction. As on 3 November 2015, the DH has received two cases of ADRs after taking febuxostat, and none of them was related to skin allergic reaction. The DH will remain vigilant on any safety update on febuxostat by other overseas drug regulatory authorities.

Recall of one batch of PMS-Zopiclone 7.5mg tablets (HK-49865)

On 7 October 2015, the DH endorsed a licensed drug wholesaler, Trenton-Boma Ltd (T-Boma), to recall one batch (batch number: 470882) of PMS-Zopiclone 7.5mg tablets at retailer level due to a quality issue.

The DH has noted that the Health Canada announced on the same day on the recall of 4 batches of PMS-Zopiclone 7.5mg tablets due to potential oversized tablets that exceed the recommended daily dose of 7.5mg could be found in the affected batches. As a precautionary measure, T-Boma was recalling the affected batch from the market.

PMS-Zopiclone 7.5mg tablets, containing zopiclone, is a prescription medicine used for the treatment of insomnia.

According to T-Boma, only one affected batch of 250 bottles of 500 tablets has been imported and has been supplied to private doctors and pharmacies since April 2013. As on 3 November 2015, the DH has not received any adverse reports in connection with the concerned product. DH will closely monitor the recall. A notice was released on the website of the Drug Office on the same day to alert the public of the recall.

Batch recall of Lescol Capsule 20mg and Lescol Capsule 40mg (HK-44854 and HK-44855)

On 20 October 2015, the DH endorsed a licensed drug wholesaler, Novartis Pharmaceuticals (HK) Limited (Novartis), to recall four batches of two pharmaceutical products, i.e. three batches of Lescol Capsule 20mg and one batch of Lescol Capsule 40mg, because of a stability issue.

Following the announcement made by Singapore HSA on 19 October 2015 that the shelf-life of Lescol Capsule 40mg would be changed from 36 months to 24 months due to a stability issue, Novartis, registration holder of Lescol Capsules in Hong Kong, conducted a recall of three batches of Lescol Capsule 20mg (batch numbers: B2001, B2008 and B2009) and one batch of Lescol Capsule 40mg (batch number: B2005) as a precautionary measure. The issue was revealed during the ongoing stability studies of the products and the manufacturer found that certain batches have failed one of the impurity tests when the products have been stored for more than 24 months. The reason is due to the stability profile of the drug substance, fluvastatin sodium, as it is susceptible towards high temperature and high humidity content in the hard gelatine capsule. The four batches under recall are all manufactured more than 24 months ago. Novartis will also apply for the change of shelf-life of the products accordingly.

Both products are prescription medicines used for the treatment of hyperlipidemia.

According to Norvatis, about 8,000 boxes of Lescol Capsule 20mg and 5,000 boxes of Lescol 40mg (both 28 capsules per box) had been supplied to the Hospital Authority (HA), private hospitals, private doctors and community pharmacies before July 2014. As on 3 November 2015, the DH has not received any adverse reports in connection with the concerned products. The DH will closely monitor the recall. A notice was released on the website of the Drug Office on the same day to alert the public of the recall.

DH endorses a batch recall of Risperdal Tab 3mg (Italy) (HK-50823)

On 20 October 2015, the DH endorsed a licensed drug wholesaler, Johnson & Johnson (Hong Kong) Limited (Johnson & Johnson), to recall one batch (batch number: EJL0N01) of Risperdal Tab 3mg (Italy) due to a labelling error.

The DH was notified by Johnson & Johnson of a customer complaint that the expiry date "09-2107" embossed on blisters of the above-mentioned batch was incorrect. The expiry date of this batch should be 09-2017, i.e. September 2017. This error only appears on the blisters, the expiry date printed on the outer box of the product is correct.

Risperdal Tab 3mg (Italy), containing risperidone, is a prescription medicine for the treatment of schizophrenia, bipolar mania and irritability

Drug Recall

associated with autistic disorder.

Johnson & Johnson reported that 3014 boxes (containing 60 tablets per box) of the affected batch had been imported. The affected batch had been supplied to the HA and exported to Macau since June 2015. As on 3 November 2015, the DH has not received any adverse reports in connection with the concerned products. The DH will closely monitor the recall. A notice was released on the website of the Drug Office on the same day to alert the public of the recall.

Drug Incident

DH urges public not to buy or consume slimming product with undeclared banned ingredients

On 13 October 2015, the DH appealed to members of the public not to buy or consume a slimming product, Nutri Drops Grapefruit Diet, as it was found to contain undeclared and banned drug ingredients which might be dangerous to health.

During the DH's market surveillance, a sample of the above product was purchased for analysis. The results from the Government Laboratory revealed that the sample contained the banned drug ingredients sibutramine and phenolphthalein.

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 increased cardiovascular risk. Phenolphthalein was used previously to treat constipation, but has been banned for its cancer-causing effect.

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.

DH raids retail shop for suspected illegal sale and possession of unregistered pharmaceutical products

On 14 October 2015, the DH raided a retail shop in Mong Kok for suspected illegal sale and possession of Part I poisons and unregistered pharmaceutical products.

Following a public complaint, it was found that the above retail shop has been offering for sale various unregistered pharmaceutical products. During the operation, various painkillers, eye drops and cold and cough medicines, all labelled in Japanese, were seized. Preliminary investigation indicated that the products were suspected to respectively contain ibuprofen, neostigmine, dihydrocodeine and methylephedrine. A Hong Kong pharmaceutical product registration number was not found on any of the products' labels.

Ibuprofen, neostigmine, dihydrocodeine and methylephedrine are Part I poisons. Side effects of ibuprofen include gastrointestinal bleeding while eye-drops with neostigmine may cause ocular pain and irritation as well as blurred vision. Side effects of methylephedrine include tachycardia, anxiety, restlessness and insomnia, while dihydrocodeine may cause nausea, vomiting and constipation.

Adverse drug reaction report of suspected Colchicine toxicity associated with drug interaction between Colchicine and Clarithromycin

On 8 October 2015, the DH issued a letter to healthcare professionals concerning suspected colchicine toxicity associated with drug interaction between colchicine and clarithromycin.

The case involved a 77 year-old woman with a history of hypertension, diabetes, gout and renal impairment. She was prescribed with colchicine for acute gouty attack, together with triple therapy (pantoprazole, clarithromycin and amoxicillin) for helicobacter associated active chronic gastritis. Five days later, the patient was admitted to hospital and subsequently found to have pancytopenia, which was compatible with the presentation of colchicine toxicity. She was later admitted to intensive care unit and her conditions gradually improved upon supportive treatment.

Colchicine has been used for the relief of acute gout and prophylaxis of acute attacks. The most frequent adverse effects of colchicine included diarrhea, nausea, vomiting and abdominal pain. Colchicine has a narrow therapeutic index and is extremely toxic in overdose. Early features of toxicity include nausea, vomiting, abdominal pain, and diarrhea. Features occurring after 1 to 7 days include confusion, decreased cardiac output, cardiac arrhythmias, renal and hepatic impairment, respiratory distress, hyperpyrexia, and bone marrow depression. These can progress in severe cases to multiple organ damage with bone marrow aplasia, convulsions, coma, rhabdomyolysis, and disseminated intravascular coagulation.

Colchicine is a substrate for P-glycoprotein and the cytochrome P450 isoenzyme CYP3A4. Inhibitors of these such as clarithromycin may increase colchicine blood concentrations and the potential for toxicity. Life-threatening or fatal colchicine toxicity has been reported with use of colchicine and clarithromycin, erythromycin, ciclosporin or calcium channel antagonists such as verapamil and diltiazem.

Healthcare professionals are advised that:

- P-glycoprotein (P-gp) or strong CYP3A4 inhibitors not be used in patients with renal or hepatic impairment who are currently taking colchicine; and
- a dose reduction or interruption of colchicine treatment be considered in patients with normal renal and hepatic function if treatment with a P-gp or a strong CYP3A4 inhibitor is required.

In Hong Kong, there are 12 registered pharmaceutical products containing colchicine. As on 3 November 2015, the DH has just received the above ADR case on colchicine. Healthcare professionals are reminded to pay attention on drug-drug interaction, and balance the risk of possible adverse effects against the benefit of treatment.

Zantac® [(Ranitidine hydrochloride Tablets) – Brown Discoloration]

On 22 October 2015, GlaxoSmithKline Limited (GSK), a licensed drug wholesaler, informed the DH about the possibility of brown discoloration present in some ranitidine tablets. GSK was going to issue letters to healthcare practitioners and investigators.

The information delivered by GSK is as follows:

Zantac® tablets are indicated for treating duodenal ulcer and benign gastric ulcer, including that associated with non-steroidal anti-inflammatory agents.

GSK would like to inform Healthcare Practitioners (HCPs) about the possibility of brown discoloration present in some ranitidine tablets. This discoloration may be present on the tablet surface or visible if a tablet is broken. Ranitidine tablets are marketed as Zantac®.

Ranitidine is known to degrade in the presence of moisture which results in a brown discoloration. The brown discoloration is due to impurities arising from the degradation of ranitidine. GSK has not been able to identify specific impurities resulting from the degradation in the brown-discoloured tablets, and are not able to confirm that the brown-

discoloured tablets meet the product safety and quality standards. No safety issues arising from brown discoloured tablets have been identified and no adverse events attributable to the brown discoloured tablets have been reported to GSK.

The incidence of these reports of brown tablets is very low. If brown-discoloured tablets are found in current product supplies, they should not be consumed as the tablet may be ineffective. If a brown tablet is found it should be returned to GSK for further testing.

These brown discoloured tablets have occurred when there is a defect in the foil of the packaging blisters and have been reported as single tablets, i.e. the other tablets in the blister pack are normal white in appearance. It is essential tablets should not be removed from their packaging until they are to be taken. HCPs on receipt of brown tablets should return all blister packaged tablets including any samples to GSK.

As a precautionary measure, GSK is now undertaking a study to understand the specific impurities arising from the brown-discolouration so as to better assess product safety and quality standards. Product information (such as product leaflets) will also be updated to stress that the tablets should not be removed from their packaging until they are to be taken.

In Hong Kong, Zantac Tab 150mg (HK-42792) and 300mg (HK-42793) are pharmaceutical products registered by GSK. GSK was going to issue a "Dear Healthcare Professional Letter" to inform the healthcare professionals of the issue on 22 October 2015. As on 3 November 2015, the DH has not received any ADR case on the product. The DH will maintain close contact with GSK to monitor any action deemed necessary and keep vigilant on any safety updates of the drug.

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.

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 1 poisons should be sold at registered pharmacies under the supervision of registered pharmacists. Illegal sale or possession of Part 1 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. Antibiotics can only be supplied at registered pharmacies by registered pharmacists or under their supervision and upon a doctor's prescription. They should only be used under the advice of a doctor. Illegal sale or possession of antibiotics are offences under the Antibiotics Ordinance (Cap 137) and the maximum penalty is a $30,000 fine and one year's imprisonment for each offence.

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: 2319 6319

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,
Wan Chai, Hong Kong

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.