Drug News
藥 物 情 報

Issue Number 105

This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in July 2018 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

The United States: FDA reinforces safety information about serious low blood sugar levels and mental health side effects with fluoroquinolone antibiotics; requires label changes

On 10 July 2018, the Food and Drug Administration (FDA) of the United States announced to strengthen the warnings in the prescribing information that fluoroquinolone antibiotics may cause significant decreases in blood sugar and certain mental health side effects. The low blood sugar levels can result in serious problems, including coma, particularly in older people and patients with diabetes who are taking medicines to reduce blood sugar. The FDA was making these changes because its recent review had found reports of life-threatening low blood sugar side effects and reports of additional mental health side effects.

FDA required the above updates in the drug labels and to the patient Medication Guides for the entire class of fluoroquinolones. This affected only the fluoroquinolone formulations taken by mouth or given by injection.

Blood sugar disturbances, including high blood sugar and low blood sugar, had already been included as a warning in most fluoroquinolone drug labels; however, FDA was adding that low blood sugar levels, also called hypoglycemia, could lead to coma.

Across the fluoroquinolone antibiotic class, a range of mental health side effects had already been described under Central Nervous System Effects in the Warnings and Precautions section of the drug label, which differed by individual drug. The new label changes would make the mental health side effects more prominent and more consistent across the systemic fluoroquinolone drug class. The mental health side effects to be added to or updated across all the fluoroquinolones are disturbances in attention, disorientation, agitation, nervousness, memory impairment, and serious disturbances in mental abilities called delirium.

FDA reviewed reports of cases submitted to FDA and the published medical literature of apparently healthy patients who experienced serious changes in mood, behavior, and blood sugar levels while being treated with systemic fluoroquinolones. Some of the mental health side effects had already been listed in some of the labels and some events listed using similar terms, but not all fluoroquinolone labels provided this information. As a result, FDA required several changes to the Warnings and Precautions section in the fluoroquinolones drug labels. Details would be added describing hypoglycemic coma, and the new subheading "Psychiatric Adverse Reactions" found under "Central Nervous System Effects" would help clarify and identify the mental health side effects.

Patients should tell their healthcare professionals if they are taking a diabetes medicine when their healthcare professional is considering prescribing an antibiotic, and also if they have low blood sugar or symptoms of it while taking a fluoroquinolone. Early signs and symptoms of low blood sugar include: confusion, dizziness, feeling shaky, unusual hunger, headaches, irritability, pounding heart or very fast pulse, pale skin, sweating,

trembling, weakness and unusual anxiety. Patients should also tell their healthcare professional immediately if they notice any changes in their mood, behavior, or thinking.

Healthcare professionals should be aware of the potential risk of hypoglycemia sometimes resulting in coma, occurring more frequently in the elderly and those with diabetes taking an oral hypoglycemic medicine or insulin. Inform patients about the risk of psychiatric adverse reactions that can occur after just one dose and stop fluoroquinolone treatment immediately if a patient reports any central nervous system side effects, including psychiatric adverse reactions, or blood glucose disturbances and switch to a non-fluoroquinolone antibiotic if possible.

In Hong Kong, as on 6 August 2018, there were 189 registered pharmaceutical products containing fluoroquinolones which were oral preparations or injectables for use in human, including ciprofloxacin (81 products), levofloxacin (62), moxifloxacin (6), norfloxacin (7), ofloxacin (31), sparfloxacin (1) and prulifloxacin (1). All products are prescription-only medicines.

As on 6 August 2018, the Department of Health (DH) had received 4 cases of adverse drug reaction related to levofloxacin and 1 case related to moxifloxacin, but these cases were not related to hypoglycemia or mental health side effects. The DH had not received any case of adverse drug reaction related to other fluoroquinolones. In light of the above FDA's announcement, the DH issued letters to inform local healthcare professionals on 11 July 2018 and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

The United Kingdom: Eltrombopag (Revolade): reports of interference with bilirubin and creatinine test results

On 17 July 2018, the Medicines and Healthcare products Regulatory Agency (MHRA) announced that there were reports of interference with bilirubin and creatinine test results associated with eltrombopag.

European Union (EU) review of data considered the available evidence of laboratory test interference (i.e., bilirubin and creatinine) associated with eltrombopag. Up to 30 Sep 2017, the licence holder of Revolade had received 9 reports worldwide of serum discolouration and interference with bilirubin and creatinine test values.

Six reports were of suspected interactions with bilirubin test values, of which 2 reported falsely low/normal bilirubin values (false-negative) despite clinically noticeable jaundice. Daily doses of eltrombopag were reported to be 75 mg in 4 cases, 150 mg in 1 case, and 300 mg in 1 case. Three reports were of suspected interactions with creatinine test values leading to falsely high/normal values (false-positive). All 3 cases of a positive interaction with serum creatinine values were in patients with paediatric severe aplastic anaemia on high doses of eltrombopag (to 5 mg/kg and 7.5 mg/kg per day; equivalent to 375 mg).

Of the 9 reported cases of interference, 2 resulted in eltrombopag dose reductions and 2 led to temporarily discontinuation of the medicine. In 1 case eltrombopag was discontinued 4 days after suspected interference with a biological test due to lack of response. Two cases did not result in eltrombopag dose reductions and the action taken with eltrombopag was not reported in the remaining 2 cases.

In addition, several publications describe potential negative interference from eltrombopag on bilirubin testing and positive interference on creatinine test values. Two publications report that eltrombopag did not interfere with aminotransferases and blood urea testing findings.

The mechanism for the eltrombopag interference with bilirubin and creatinine test values appears to be pH-dependent and method- or reagent-specific and related to the colour of eltrombopag in serum. The false-positive interference with creatinine may result in a misleading clinical picture of apparent renal deterioration. The interference with bilirubin is less likely to have clinically significant consequences since the stopping criteria for hepatic disorders are based on rises in serum alanine aminotransferase (ALT) levels and clinical symptoms/evidence of hepatic decompensation, rather than bilirubin values alone.

Healthcare professionals are advised:

- Eltrombopag is highly coloured (reddish-brown) and can cause serum discolouration and interference with the test results of creatinine and bilirubin.
- Be aware that interference with bilirubin (falsely low/normal results) and creatinine (falsely high/ normal results) may occur in patients taking eltrombopag.
- If bilirubin and/or creatinine laboratory results are inconsistent with clinical observations, request re-testing using another method to determine the validity of the result.
- The laboratory may consider susceptibility to serum discolouration and other factors that may be relevant when selecting an alternative test method.
- Report suspected adverse drug reactions, including any harm that occurs from a medicine interfering with laboratory test results, to the Yellow Card Scheme.

In Hong Kong, as on 6 August 2018, there were 4 registered pharmaceutical products containing eltrombopag, namely Revolade Tab 25mg (HK-60349), Revolade Tab 50mg (HK-60350), Revolade Tablets 25mg (Spain) (HK-62055) and Revolade Tablets 50mg (Spain) (HK-62056). All products are registered by Novartis Pharmaceuticals (HK) Limited, and are prescription -only medicines. As on 6 August 2018, the DH had received 10 cases of adverse drug reaction related to eltrombopag, but these cases were not related to interference with bilirubin and creatinine test results. In light of the above MHRA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 18 July 2018. The DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

The United Kingdom: Pressurised metered dose inhalers (pMDI): risk of airway obstruction from aspiration of loose objects

On 17 July 2018, the MHRA announced that it received reports on patients using pressurised metered dose inhalers (pMDI) who inhaled objects into the back of the throat, resulting in coughing. In some cases, objects were aspirated, causing airway obstruction.

Since 1987, MHRA had received 22 reports from Yellow Cards and other sources of accidental inhalation of the mouthpiece cover or objects that became trapped in the inhaler after dispensing when stored by patients. Additionally, MHRA was aware of 36 cases reported outside of the United Kingdom. Loose/foreign objects reported in these cases included tissues, stickers, coins, and plastic items. Some incidents resulted in pharyngeal injury, temporary asphyxiation, or surgical removal of aspirated objects. One patient experienced a pneumothorax.

Recently, MHRA received a report in which a foreign body was aspirated; it became lodged in the bronchus causing granulation and had to be removed bronchoscopically.

Healthcare professionals are advised:

- Train patients in the correct use of their inhaler; instructions for patients are provided in the patient information leaflet.
- Tell patients to remove the mouthpiece cover fully, shake the inhaler to remove loose objects that may not be visible, and check the inside and outside of the mouthpiece are clear before inhaling a dose.
- To prevent objects entering the mouthpiece during storage, remind patients to replace the cover immediately after use, ensuring it clicks into place.
- Pharmacists dispensing a pMDI should emphasise to patients the need to clean the device regularly by following the instructions in the patient leaflet and to inspect the device for signs of damage; devices that are damaged should be replaced immediately.
- Continue to report adverse incidents during use of inhalers, as well as suspected adverse reactions to the medicine, on a Yellow Card.

In Hong Kong, as on 6 August 2018, there were 43 registered pharmaceutical products which were pressurised inhalers; and the DH had not received any case of adverse drug reaction related to aspiration of foreign body when using the above inhaler products. Patients are advised to follow the instructions provided in the product information for correct use of their inhaler, and consult healthcare professionals if they are in doubt or feeling unwell. The DH will remain vigilant on safety update of the products issued by other overseas drug regulatory authorities.

The United Kingdom: Darunavir boosted with cobicistat: avoid use in pregnancy due to risk of treatment failure and maternal-to-child transmission of HIV-1

On 17 July 2018, the MHRA announced that new pharmacokinetic data showed mean exposure of darunavir (brand name Prezista) boosted with cobicistat (available in combination in Rezolsta▼, Symtuza▼) to be lower during the second and third trimesters of pregnancy than during 6 to 12 weeks postpartum. Low darunavir exposure might be associated with an increased risk of treatment failure and an increased risk of HIV-1 transmission to the unborn child.

New pharmacokinetic data based on 6 women enrolled in a Phase 3b study (TMC114HIV3015) showed lower mean exposure (AUC) levels of darunavir boosted with cobicistat (darunavir/ cobicistat) during the second trimester (56% lower) and third trimester (50% lower) of pregnancy, compared with 6 to 12 weeks postpartum. Mean darunavir Cmin concentrations were around 90% lower during the second and third trimesters of pregnancy than during 6 to 12 weeks postpartum. Exposure of cobicistat was 63% lower during the second trimester and 49% lower during the third trimesters of pregnancy than during 6 to 12 weeks postpartum.

Low darunavir exposure might be associated with an increased risk of treatment failure and an increased risk of HIV-1 transmission to the child. Mother-to-child transmission did not occur in any of the 6 infants born to the 6 mothers who delivered during study and completed the study. So far, the advice was precautionary, and MHRA was not aware of any clinical pattern to suggest that patient safety had been affected.

The product information for Prezista (darunavir), Rezolsta▼ (darunavir and cobicistat) and Symtuza▼ (darunavir, cobicistat, emtricitabine, tenofovir alafenamide) would be updated to recommend against use of darunavir/cobicistat in pregnancy.

Healthcare professionals are advised:

- Pharmacokinetic data show low exposure values of darunavir boosted with cobicistat (darunavir/ cobicistat) during the second and third trimesters of pregnancy.
- Low darunavir exposure may be associated with an increased risk of treatment failure and an increased risk of mother-to-child transmission of HIV infection.
- Therapy with darunavir/cobicistat should not be initiated during pregnancy.
- Switch women who are pregnant and taking darunavir/cobicistat to an alternative regimen: darunavir/ritonavir may be considered as an alternative.
- Report suspected adverse drug reactions with HIV medicines to the Yellow Card Scheme, including treatment failure that results in harm.

In Hong Kong, as on 6 August 2018, there were 3 registered pharmaceutical products containing darunavir only, 1 product containing darunavir combined with cobicistat, and 3 products containing cobicistat combined with other drug ingredients. All products are prescription-only medicines. As on 6 August 2018, the DH had not received any case of adverse drug reaction related to darunavir or cobicistat. In light of the above MHRA's announcement, the DH issued letters to inform local healthcare professionals on 18 July 2018, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Australia: Sodium glucose co-transporter 2 inhibitors: Safety advisory - diabetic ketoacidosis and surgical procedures

On 18 July 2018, the Therapeutic Goods Administration (TGA) advised consumers and healthcare professionals that it was working with sponsors of sodium glucose co-transporter 2 (SGLT2) inhibitors to update medicine information documents to strengthen warnings about the risk of diabetic ketoacidosis with these medicines. In particular, the risk was increased in people who would undergo surgical or medical procedures. This action had been prompted by an increase in the number of local reports received by the TGA of diabetic ketoacidosis occurring in people being treated with these medicines in Australia. SGLT2 inhibitors that had been marketed in Australia included dapagliflozin and empagliflozin.

There is a known association between treatment with SGLT2 inhibitors and diabetic ketoacidosis and there is information about this potential side effect in the Product Information and Consumer Medicine Information documents for these products. Diabetic ketoacidosis is an acute complication of diabetes, in which substances called ketone bodies build up in the blood. Early signs and symptoms of diabetic ketoacidosis, typically developed over 24 hours, include abdominal pain, nausea, vomiting, anorexia (loss of appetite), excessive thirst, difficult breathing, unusual fatigue and sleepiness. It typically presents with high glucose levels, however atypical diabetic ketoacidosis occurring at lower levels of blood glucose, known as 'euglycaemic ketoacidosis', may also occur. If diabetic ketoacidosis is not diagnosed early and treatment initiated, more serious signs and symptoms including dehydration, deep gasping breathing, confusion and coma can potentially develop.

TGA continued to receive reports of diabetic ketoacidosis, including some reports of 'euglycaemic ketoacidosis'. A number of reports involved patients who had undergone a surgical operation or a medical procedure requiring anaesthesia or light sedation, including cardiovascular, bariatric, orthopaedic or gastrointestinal procedures. Reports received by the TGA also included cases in which patients with type 1 diabetes had been prescribed an SGLT2 inhibitor. SGLT2 inhibitors were not registered for use in patients with type 1 diabetes. Risk factors in other cases included patients experiencing acute illness, such as infections, gastrointestinal conditions, cardiovascular conditions, dehydration, malnourishment/reduced caloric intake and non-adherence with insulin or reductions in insulin dose.

In Hong Kong, as on 6 August 2018, there were 17 registered pharmaceutical products containing SGLT2 inhibitors, including dapagliflozin (5 products), canagliflozin (2 products) and empagliflozin (10 products). All products are prescription-only medicines. As on 6 August 2018, the DH had received 3 cases of adverse drug reaction of diabetic ketoacidosis related to SGLT2 inhibitors: dapagliflozin (1 case), canagliflozin (1 case) and empagliflozin (1 case). News related to diabetic ketoacidosis of SGLT2 inhibitors was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue Nos. 67, 74, 76 and 88. In Feb 2017, the Registration Committee of the Pharmacy and Poisons Board discussed the matter and decided that the package insert of products containing SGLT2 inhibitors should include safety information on the risk of diabetic ketoacidosis. The DH will remain vigilant on safety update of the drugs issued by other overseas drug regulatory authorities.

Canada: Summary Safety Review - Sodium/ glucose cotransporter 2 (SGLT2) inhibitors - Assessing the potential risk of inflammation of the pancreas (acute and chronic pancreatitis)

On 20 July 2018, Health Canada announced that it had reviewed the potential risk of pancreatitis with the use of sodium/glucose cotransporter 2 (SGLT2) inhibitors (dapagliflozin, canagliflozin and empagliflozin) because of Canadian reports and case reports published in the scientific literature that indicated a possible link.

At the time of the review, Health Canada had received 20 Canadian reports of acute pancreatitis related to the use of SGLT2 inhibitors and no reports of chronic pancreatitis. Of these reports, 1 was further assessed as it met the criteria defined for this review. This Canadian report showed a possible link between acute pancreatitis and the use of an SGLT2 inhibitor. The review also looked at 476 international reports and 6 published cases of pancreatitis related to the use of SGLT2 inhibitors. Of these reports, 28 cases of acute pancreatitis, but no cases of chronic pancreatitis, were further assessed as they met the criteria defined for this review. Of the 28 reports, 18 showed a possible link between acute pancreatitis and the use of a SGLT2 inhibitor. In most of the remaining reports, other medical conditions and medications could have caused the pancreatitis. A review of the scientific literature did not find any published studies that showed an increased risk of pancreatitis in patients treated with SGLT2 inhibitors.

Health Canada's review of the available information concluded that there may be a link

between the use of SGLT2 inhibitors and the risk of acute pancreatitis. However, there was limited evidence to suggest a link with chronic pancreatitis. Health Canada was working with the manufacturers to update the product safety information for SGLT2 inhibitors to inform healthcare professionals and patients about this risk.

In Hong Kong, as on 6 August 2018, there were 17 registered pharmaceutical products containing SGLT2 inhibitors, including dapagliflozin (5 products), canagliflozin (2 products) and empagliflozin (10 products). All products are prescription-only medicines. As on 6 August 2018, the DH had received 3 cases of adverse drug reaction related to dapagliflozin, 2 cases related to canagliflozin and 1 case related to empagliflozin, but these cases were not related to pancreatitis. In light of the above Health Canada's announcement, the DH issued letters to inform local healthcare professionals on 24 July 2018, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Canada: Summary Safety Review - Remicade (infliximab) - Assessing the potential risk of a blistering skin condition known as linear IgA bullous dermatosis

On 23 July 2018, Health Canada announced that it had reviewed the potential risk of a blistering skin condition known as linear IgA bullous dermatosis with the use of Remicade, following published reports of this risk in patients treated with Remicade.

At the time of the review, Health Canada had received 1 Canadian report of a blistering skin condition in a patient treated with Remicade. This report showed that there was a potential link between the use of Remicade and the blistering skin condition. The safety review also looked at information from 6 case reports (including the Canadian report) provided by the manufacturer of Remicade. It was determined that, in 4 of these cases, the blistering skin disease was potentially related to the Remicade treatment, while the remaining 2 cases could not be assessed due to missing information. Review of data from these cases and the scientific literature supported a possible link between the use of Remicade and the risk of the blistering skin condition. Since the blistering skin condition has only been reported in a small number of patients using Remicade, it is concluded that the risk of it happening with the use of the drug is rare.

Health Canada's review of the available information concluded that there might be a link between the use of Remicade and the risk of linear IgA bullous dermatosis. Health Canada had already worked with the manufacturer of Remicade to update the product safety information to include the risk of this blistering skin condition.

In Hong Kong, Remicade For Inj 100mg (HK-54964) is a pharmaceutical product registered by Johnson & Johnson (Hong Kong) Ltd, and is a prescription-only medicine. As on 6 August 2018, the DH had received 4 cases of adverse drug reaction related to Remicade, but these cases were not related to linear IgA bullous dermatosis. In light of the above Health Canada's announcement, the DH issued letters to inform local healthcare professionals on 24 July 2018, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Canada: Summary Safety Review - Imbruvica (ibrutinib) - Assessing the potential risk of a serious and life-threatening abnormal heart rhythm (ventricular tachyarrhythmia)

On 26 July 2018, Health Canada announced that it had reviewed the potential risk of a type of abnormal heart rhythm called ventricular tachyarrhythmia with the use of ibrutinib following the publication of an article describing a potential link.

At the time of the review, Health Canada had received 5 Canadian reports of ventricular tachyarrhythmia suspected to be linked to ibrutinib. Of these reports, 1 was further assessed as it met the criteria for this review. This Canadian report showed a likely link between ibrutinib and ventricular tachyarrhythmia. The review also looked at 150 international reports of ventricular tachyarrhythmia suspected to be linked to ibrutinib. Of these reports, 23 were further assessed as they met the criteria for this review. Of the 23 reports, 3

showed a likely link and 20, with one reporting death, were found to have a possible link between ibrutinib and ventricular tachyarrhythmia. In 9 of the 24 cases that were looked at (1 Canadian and 23 international), other factors could have played a role in the ventricular tachyarrhythmia such as the patient's medical history and other medications used. Product safety information of ibrutinib in the United States, Europe and New Zealand had been updated to include ventricular tachyarrhythmia. In addition, the United Kingdom published a safety communication on the risk of ventricular tachyarrhythmia with ibrutinib.

Health Canada's review of the available information found that there might be a link between ibrutinib and ventricular tachyarrhythmia. Health Canada had already worked with the manufacturer of ibrutinib to update the product safety information to include ventricular tachyarrhythmia.

In Hong Kong, as on 6 August 2018, there were 2 registered pharmaceutical products containing ibrutinib, namely Imbruvica Capsules 140mg (HK-64088) and Imbruvica Capsules 140mg (HK-65397). Both products are registered by Johnson & Johnson (Hong Kong) Ltd, but manufactured in different site, and are prescription-only medicines. As on 6 August 2018, the DH had received 9 cases of adverse drug reaction related to ibrutinib, but these cases were not related to ventricular tachyarrhythmia.

Related news was previously issued by MHRA, and was reported in the Drug News Issue No. 94. Letters to inform local healthcare professionals of the risk of ventricular tachyarrhythmia of the drug was issued by the DH on 16 Aug 2017. In Dec 2017, the Registration Committee of the Pharmacy and Poisons Board discussed the matter and decided that the package insert of the drug should include safety information on the risk of ventricular tachyarrhythmia. The DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

European Union: EMA restricts use of prostate cancer medicine Xofigo. Medicine to be used only after two previous treatments or when other treatments cannot be taken

On 27 July 2018, the European Medicines Agency (EMA) concluded its review of the cancer medicine Xofigo (radium-223 dichloride), and recommended restricting its use to patients who had already two previous treatments for metastatic prostate cancer (prostate cancer that spread to the bone) or who could not receive other treatments.

Xofigo must also not be used with the medicines Zytiga (abiraterone acetate) and the corticosteroid prednisone or prednisolone. Xofigo should not be used with other systemic cancer therapies, except for treatments to maintain reduced levels of male hormones (hormone therapy). The medicine should also not be used in patients who have no symptoms, in line with the current indication; in addition, the use of Xofigo is not recommended in patients with a low number of bone metastases called osteoblastic bone metastases.

The review of Xofigo was carried out by EMA's Pharmacovigilance Risk Assessment Committee (PRAC) after data from a clinical study suggested that patients given Xofigo in combination with Zytiga and prednisone/prednisolone could be at risk of dying earlier and had more fractures than patients given placebo (a dummy treatment) with Zytiga and prednisone/prednisolone. The study included patients with no or only mild symptoms, whereas Xofigo was only authorised in patients with symptoms. In addition, the combination used in this study is now contraindicated. In the study, patients given the combination with Xofigo died on average 2.6 months earlier than those given the combination with placebo. In addition, 29% of patients who received the Xofigo combination had fractures, compared with 11% of patients given the placebo combination.

It is thought that Xofigo, which is taken up by the bone, accumulates at sites where the bone is already damaged, for example by osteoporosis or micro-fractures, increasing the risk of fracture. However, the reasons for a possible earlier death seen in this study are not fully understood. The company that markets Xofigo will have to conduct studies to further characterise these events and clarify the mechanisms behind them.

The PRAC's recommendations had been endorsed by EMA's Committee for Medicinal Products for

Human Use (CHMP) and would be sent to the European Commission for a final legal decision.

In Hong Kong, Xofigo Solution for Injection 1100 KBQ/ml (HK-64332) is a pharmaceutical product containing radium-223 dichloride which is registered by Bayer Healthcare Ltd, and is a prescription-only medicine. As on 6 August 2018, the DH had received 11 cases of adverse drug reaction related to Xofigo, but none of them were related to death and fractures. Related news was previously issued by various overseas drug regulatory authorities, and was reported in Drug News Issue Nos. 98 and 101. Letters to inform local healthcare professionals were issued on 16 Jul 2018. In light of the EMA's endorsement of PRAC's recommendation, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Drug Recall

DH instructed recall of five valsartan-containing products

On 6 July 2018, DH instructed two licensed medicine wholesalers, namely Actavis Hong Kong Limited (Actavis) and Hong Kong Medical Supplies Ltd (HK Medical), to recall the following products:-

Product	Hong Kong Registration Number	Registration certificate holder
Valtensin 160mg tablets	HK-61786	Actavis
Valtensin 80mg tablets	HK-61787	Actavis
Valtensin HCT tablets 160/12.5mg	HK-61784	Actavis
Valtensin HCT tablets 80/12.5mg	HK-61785	Actavis
Valsartan Stada 80mg tablets	HK-60794	HK Medical

The DH through its surveillance system noted that the raw material valsartan produced by a manufacturer (Zhejiang Huahai Pharmaceutical Co., Ltd 浙江華海藥業股份有限公司; abbreviated: Zhejiang Huahai) in the Mainland and used in certain pharmaceutical products as active ingredient, was found to contain an impurity N-nitrosodimethylamine (NDMA). NDMA is classified as a probable human carcinogen based on results from laboratory tests.

Various countries in Europe and Asia are in the process of recalling the affected products from the market. According to the investigation of the European regulatory agency, the presence of NDMA is unexpected and believed to be related to the change of production method of the valsartan raw material since July 2012. A preliminary assessment from Europe estimated that, based on extrapolation from animal studies, there could be one extra case of cancer for every 5,000 patients taking the affected medicines at the highest valsartan dose (320mg) every day for 7 years. For details, please refer to http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/08/news_detail_003000.jsp&mid=WC0b01ac058004d5c1

There are countries which announced recall of the affected products from their market. In July, the World Health Organization (WHO) raised alerts on the issue and advised that there may be a shortage of valsartan products due to the incident. For details, please refer to https://www.pharmacy.moh.ps/Content/File/BO7cBuvjJdFCgOAjS4tadawq_RIPnQIHnzV6VebvzAAlLbi6Y.pdf

In Hong Kong, as on 6 August 2018, there were a total of 84 registered pharmaceutical products that contain valsartan as active ingredient. As confirmed, the captioned listed 5 recalled products are made from raw material supplied by the Zhejiang Huahai.

According to Actavis and HK Medical, the above 5 recalled products had been supplied to local doctors and pharmacies. The products Valtensin 80mg and 160mg tablets had also been supplied to the Hospital Authority. Both companies have set up hotlines (Actavis: 3188 4288; HK Medical: 2806 3112) to answer related enquiries.

As on 6 August 2018, the DH had not received any adverse reactions related to the affected products. It is noted that the European regulatory agency is conducting an evaluation on the issue, including the health impacts to patients. The DH will closely monitor the assessment results

It is expected that the NDMA in the affected products will not cause acute toxicity or immediate health risks. Patients who are taking the above products should not stop taking the medicines, but should seek advice from their healthcare professionals as soon as possible for proper arrangement

According to the information provided by local suppliers, there are stocks of unaffected valsartan products available in Hong Kong.

The DH has provided update information at Drug Office's website (www.drugoffice.gov.hk) and will remain vigilant on any safety update related to the impurity NDMA contained in valsartan products.

DH endorsed a batch recall of Bon-One Tab 0.25mcg

On 20 July 2018, DH endorsed a licensed drug wholesaler, Hind Wing Co. Ltd., to recall one batch (batch number: 5125) of Bon-One Tab 0.25mcg (registration number: HK-49190) as a precautionary measure.

The DH was notified by Hind Wing that the manufacturer of the product in Japan found that one 0.5mcg tablet engraved with "0.5" was packed in a blister pack of the concerned batch of the Bon-One Tab 0.25mcg product.

Bon-One Tab 0.25mcg, containing alfacalcidol, is a prescription-only medicines used for treatment of symptoms associated with abnormal vitamin D metabolism and osteoporosis. According to Hind Wing, about 200 boxes (containing 100 tablets per box) of the affected batch had been supplied to private doctors and pharmacies since Feb 2018.

As on 6 August 2018, the DH had not received any adverse reaction reports related to the product. Members of the public should consult healthcare providers if in doubt after taking the product.

Hind Wing has set up a hotline (2566 0562) to answer any public enquiries; and as on 6 August 2018 the recall had already been completed. A notice was posted on the Drug Office website on 20 July 2018 to alert the public of the product recall.

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.

Under the Import and Export Ordinance (Cap. 60), pharmaceutical products must be imported or exported under and in accordnance with an import or export licence issued under the Import and Export Ordinance. Illegal import or export of pharmaceutical products are offences under the Import and Export Ordinance (Cap. 60) and the maximum penalty is a fine of $500,000 and 2 years' imprisonment.

Update on Drug Office's website: You can now search the newly registered medicines in the past year at http://www.drugoffice.gov.hk/eps/drug/newsNRM60/en/healthcare_providers?pageNoRequested=1.
Details of ALL registered pharmaceutical products can still be found in the Drug Office website at http://www.drugoffice.gov.hk/eps/do/en/healthcare_providers/news_informations/reListRPP_index.html.

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,
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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.