Drug News
藥 物 情 報

Issue Number 109

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

Canada: XOFIGO (radium Ra 223 dichloride) - Increased incidence of fractures and trend for increased deaths with XOFIGO used in combination with abiraterone and prednisone/prednisolone

On 8 November 2018, Health Canada announced that an increased incidence of fractures and a trend for increased deaths was observed in a clinical trial assessing the concurrent initiation of XOFIGO in combination with abiraterone acetate and prednisone/prednisolone in the treatment of asymptomatic or mildly symptomatic chemotherapy-naïve patients with bone predominant metastatic castration-resistant prostate cancer.

This risk communication relates to an investigational study. An increased incidence of fractures and a trend for increased deaths was observed in a randomised, double-blind, placebo-controlled, and multicenter Phase III clinical study (ERA-223 study). This clinical study was conducted to investigate the efficacy and safety of XOFIGO or placebo, concurrently initiated in combination with abiraterone acetate and prednisone/prednisolone in the treatment of asymptomatic or mildly symptomatic chemotherapy-naïve patients with bone predominant metastatic castration-resistant prostate cancer. The study was unblinded early following an Independent Data Monitoring Committee review having observed increased fractures and death incidents. In December 2017, Bayer Inc. independently communicated this important safety information to Canadian healthcare professionals.

The primary analysis of the ERA-223 study results has now been completed. An increased incidence of fractures (28.6% vs 11.4%) and a trend for increased deaths (38.5% vs 35.5%) was observed among patients receiving XOFIGO in combination with abiraterone acetate plus prednisone/prednisolone, compared to patients receiving placebo in combination with abiraterone acetate plus prednisone/prednisolone.

XOFIGO in combination with abiraterone acetate and prednisone/prednisolone is not authorized in Canada for the treatment of metastatic castration-resistant prostate cancer.

Healthcare professionals are reminded that:

- XOFIGO is authorized in Canada for the treatment of patients with castration-resistant prostate cancer with symptomatic bone metastases and no known visceral metastatic disease. This indication of XOFIGO remains unchanged.
- XOFIGO is not recommended for use in combination with abiraterone acetate plus prednisone/prednisolone.
- Safety and efficacy with the combination of XOFIGO and agents other than gonadotropin-releasing hormone analogues have not been established.

Health Canada in collaboration with Bayer Inc. has updated the XOFIGO Canadian Product Monograph.

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 Limited and is a

prescription-only medicine. As of 5 December 2018, the Department of Health (DH) has received 11 cases of adverse drug reaction (ADR) related to Xofigo, but none of them is related to death and fractures. Related news was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 98, 101 and 105. The DH issued a letter to inform local healthcare professionals to draw their attention on 16 July 2018. The matter has been discussed by the Registration Committee of the Pharmacy and Poisons Board (the Registration Committee) on 12 December 2018 and decided that the sales pack / package insert should include the safety information on restrictions on the use of the medicine due to increased risk of fracture and trend for increased mortality seen in clinical trial.

UK: Hydrochlorothiazide: risk of non-melanoma skin cancer, particularly in long-term use

On 14 November 2018, the Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom (UK) announced that pharmacoepidemiological studies have shown a dose-dependent increased risk of non-melanoma skin cancer (basal cell carcinoma [BCC] and squamous cell carcinoma [SCC], including SCC lip cancer) with exposure to increasing cumulative doses of hydrochlorothiazide.

Two recent pharmacoepidemiological studies in Danish nationwide data sources (including the Danish Cancer Registry and National Prescription Registry) have shown a cumulative, dose-dependent, association between hydrochlorothiazide and non-melanoma skin cancer. The known photosensitising actions of hydrochlorothiazide could act as possible mechanism for this risk. The study authors' analyses did not find a similar association for risk of BCC or SCC and SCC lip cancer with overall or cumulative use of other diuretics and other hypertensives, including bendroflumethiazide, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, and furosemide. Pedersen and colleagues reported that, assuming causality, 9 in 100 SCC cases and fewer than 1 in 100 BCC cases that were diagnosed during the study period may have been attributed to hydrochlorothiazide use. Pottegård and colleagues reported that 11 in 100 of SCC lip cancer cases occurring in the study period may have been attributed to hydrochlorothiazide use.

Based on the results of the two Danish epidemiological studies, a best estimate of the increased risk is 7.7-fold for SCC and 1.5-fold for BCC based on a length of usage of hydrochlorothiazide 12.5mg daily for 44 years or 25 mg daily for 22 years. For hypertension, products containing 25 mg of hydrochlorothiazide are indicated only if patients are not adequately controlled on lower-dose products.

The Summary of Product Characteristics and Patient Information Leaflets for all the concerned products have been updated to inform of the risk of non-melanoma skin cancer.

Healthcare professionals are advised:

- inform patients taking hydrochlorothiazide-containing products of the risk of non-melanoma skin cancer, particularly in long-term use, and advise them to regularly check for and report any new or changed skin lesions or moles.
- reconsider the use of hydrochlorothiazide in patients who have had previous skin cancer.
- examine all suspicious moles or skin lesions (potentially including histological examination of biopsies).
- advise patients to limit their exposure to sunlight and ultraviolet (UV) rays and use adequate protection when exposed to sunlight and UV rays to minimise the risk of skin cancer.

In Hong Kong, there are 104 registered pharmaceutical products containing hydrochlorothiazide, and all products are prescription-only medicines. As of 5 December 2018, the DH has received 2 cases of ADR related to hydrochlorothiazide, but these cases are not related to skin cancer. In light of the above MHRA's announcement, the DH issued a letter to inform local healthcare professionals to draw their attention on 15 November 2018 and the matter will be discussed by the Registration Committee.

UK: Systemic and inhaled fluoroquinolones: small increased risk of aortic aneurysm and dissection; advice for prescribing in high-risk patients

On 14 November 2018, the MHRA announced that systemic (by mouth or injection) and inhaled fluoroquinolones may be associated with a small increased risk of aortic aneurysm and dissection, particularly in older patients.

Data from epidemiologic and non-clinical studies indicate an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones. Epidemiological studies suggest an increased risk of aortic aneurysm and dissection with fluoroquinolone usage, particularly in older patients. One study reported a rate of aortic aneurysm or dissection of 1.2 cases per 1000 person-years among fluoroquinolone treatment episodes versus 0.7 cases per 1000 person-years among amoxicillin treatment episodes, corresponding to an estimated absolute difference of 82 (95% confidence interval 15–181) cases of aortic aneurysm or dissection by 60 days per 1 million treatment episodes. Another study of patients aged 65 years and older in Canada reported a rate of aortic aneurysms diagnosed in hospital and emergency departments as 3.5 per 1000 person-years for patients currently using fluoroquinolones versus 1.3 per 1000 person-years for patients not using fluoroquinolones.

In the studies, the increased risk for aortic aneurysm was seen within the first 1 to 2 months of treatment with systemic fluoroquinolones. The data do not allow for differentiation between risk for different fluoroquinolones or durations of treatment. These findings indicate that systemic or inhaled fluoroquinolones might contribute to aortic aneurysm and dissection, in particular in patients with pre-existing risk factors.

Healthcare professionals are advised:

- fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients at risk for aortic aneurysm and dissection.
- conditions predisposing to aortic aneurysm and dissection include:
  - a family history of aneurysm disease
  - diagnosis with pre-existing aortic aneurysm and/or aortic dissection
  - other risk factors or conditions predisposing for aortic aneurysm and dissection (for example, Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, and known atherosclerosis).
- advise patients, particularly elderly people and those at risk, about rare events of aortic aneurysm and dissection and of the importance of seeking immediate medical attention in case of sudden-onset severe abdominal, chest or back pain.

In Hong Kong, there are 188 registered pharmaceutical products containing fluoroquinolones which are oral preparations or injectables for use in human, including ciprofloxacin (81 products), levofloxacin (62 products), moxifloxacin (6 products), norfloxacin (7 products), ofloxacin (30 products), sparfloxacin (1 product) and prulifloxacin (1 product). All products are prescription-only medicines. As of 5 December 2018, the DH has received 4 cases of ADR related to levofloxacin and 1 case related to moxifloxacin, but these cases are not related to aortic aneurysm and dissection. The DH has not received any case of ADR related to other fluoroquinolones. In light of the above MHRA's announcement, the DH issued a letter to inform local healthcare professionals to draw their attention on 15 November 2018. The DH will remain vigilant on safety update of the drugs issued by other overseas drug regulatory authorities.

UK: Sildenafil (Revatio and Viagra): reports of persistent pulmonary hypertension of the newborn (PPHN) following in-utero exposure in a clinical trial on intrauterine growth restriction

On 14 November 2018, the MHRA announced that data from an independent clinical trial has shown potential harm, including increased risk of PPHN and increased mortality, when sildenafil is used in pregnancy for early-onset intrauterine growth

restriction (IUGR).

Interim data from an independent clinical trial, the Dutch STRIDER (Sildenafil TheRapy in Dismal prognosis Early-onset fetal growth Restriction) study, suggest an increased risk of PPHN and neonatal mortality when sildenafil was used in pregnancy for intrauterine (fetal) growth restriction compared with placebo. The group assigned to sildenafil had an incidence of 17 cases of PPHN in 64 babies (27%), including 11 deaths before discharge. In the placebo group, 3 of 58 babies (5%) had PPHN, with no reported deaths before discharge. These findings occurred in the absence of any benefit shown on the primary endpoint of neonatal survival until term age.

The Dutch STRIDER study was one of 5 independent studies by an international collaboration investigating the use of sildenafil for this unauthorised use. The 5 trials in the STRIDER Consortium were undertaken in the UK, Ireland, The Netherlands, New Zealand/Australia, and Canada. Pregnant women were randomised to generic sildenafil or placebo. Sildenafil was given in a dose of 25 mg three times a day to pregnant women for the treatment of severe intrauterine (fetal) growth restriction.

Details of the interim analysis of the Dutch STRIDER study are not yet available and the analysis by the STRIDER consortium of studies is awaited. A letter has been sent to relevant healthcare professionals to inform them of this information and that sildenafil should not be used in intrauterine (fetal) growth restriction.

Healthcare professionals are advised:

- sildenafil (Revatio and Viagra) is not authorised for the treatment of IUGR.
- Revatio for the treatment of pulmonary arterial hypertension is not recommended in pregnancy unless strictly necessary; Viagra is not authorised for use in women.

In Hong Kong, there are 82 registered pharmaceutical products containing sildenafil, and all products are prescription-only medicines. As of 5 December 2018, the DH has received 2 cases of ADR related to sildenafil, but these cases are not related to PPHN. In light of the above MHRA's announcement, the DH issued a letter to inform local healthcare professionals to draw their attention on 15 November 2018. The DH will remain vigilant on the conclusion of the study and safety update of the drug issued by other overseas drug regulatory authorities.

Singapore: Imovane (zopiclone) Tablet 7.5mg: restriction of indications

On 15 November 2018, the Health Sciences Authority of Singapore announced that Sanofi-aventis would like to inform healthcare professionals about the new restriction of the indication to "short-term" treatment of insomnia and additional recommendations on the duration of treatment. These risk minimisation measures are intended to promote the proper use of zopiclone and limit the risk of abuse and drug dependence. The Imovane package insert in Singapore has been updated with the above information.

In Hong Kong, there are 30 registered pharmaceutical products containing zopiclone, and all products are prescription-only medicines. As of 5 December 2018, the DH has received 2 cases of ADR related to zopiclone, but these cases are not related to abuse and drug dependence. Recommendation on short-term use of the drug and the risk of dependence are documented in reputable drug references such as Martindale: The Complete Drug Reference. The DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

EU: Disabling and potentially permanent side effects lead to suspension or restrictions of quinolone and fluoroquinolone antibiotics

On 16 November 2018, the European Medicines Agency (EMA) of the European Union (EU) announced that it has reviewed the serious, disabling and potentially permanent side effects with quinolone and fluoroquinolone antibiotics given by mouth, injection or inhalation. The review incorporated the views of patients, healthcare professionals and academics presented at the EMA's public hearing on fluoroquinolone and quinolone antibiotics in June 2018.

The EMA's Committee for Medicinal Products for Human Use (CHMP) has endorsed its Pharmacovigilance Risk Assessment Committee's (PRAC) recommendations and concluded that the marketing authorization of medicines containing cinoxacin, flumequine, nalidixic acid, and pipemidic acid should be suspended.

The CHMP confirmed that the use of the remaining fluoroquinolone antibiotics should be restricted. In addition, the prescribing information for healthcare professionals and information for patients will describe the disabling and potentially permanent side effects and advise patients to stop treatment with a fluoroquinolone antibiotic at the first sign of a side effect involving muscles, tendons or joints and the nervous system.

Restrictions on the use of fluoroquinolone antibiotics will mean that they should **not** be used:

- to treat infections that might get better without treatment or are not severe (such as throat infections);
- to treat non-bacterial infections, e.g. non-bacterial (chronic) prostatitis;
- for preventing traveller's diarrhoea or recurring lower urinary tract infections (urine infections that do not extend beyond the bladder);
- to treat mild or moderate bacterial infections unless other antibacterial medicines commonly recommended for these infections cannot be used.

Importantly, fluoroquinolones should generally be **avoided** in patients who have previously had serious side effects with a fluoroquinolone or quinolone antibiotic. They should be used **with special caution** in the elderly, patients with kidney disease and those who have had an organ transplantation because these patients are at a higher risk of tendon injury. Since the use of a corticosteroid with a fluoroquinolone also increases this risk, combined use of these medicines should be avoided.

<u>Information for patients</u>

- Fluoroquinolone medicines (which contain ciprofloxacin, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin, ofloxacin, pefloxacin, prulifloxacin and rufloxacin) can cause long-lasting, disabling and potentially permanent side effects involving tendons, muscles, joints and the nervous system.
- These serious side effects include inflamed or torn tendon, muscle pain or weakness, and joint pain or swelling, walking difficulty, feeling pins and needles, burning pain, tiredness, depression, problems with memory, sleeping, vision and hearing, and altered taste and smell.
- Tendon swelling and injury may occur within 2 days of starting treatment with a fluoroquinolone but may even occur several months after stopping treatment.
- Stop taking a fluoroquinolone medicine and contact your doctor at once in the following cases:
  - ➢ at the first sign of tendon injury, such as tendon pain or swelling – rest the painful area;
  - ➢ if you get pain, feel pins and needles, tingling, tickling, numbness or burning, or weakness especially in the legs or arms;
  - ➢ if you get swelling in the shoulder, arms or legs, have walking difficulty, feel tired or depressed or have problems with your memory or with sleeping or you notice changes with your vision, taste, smell or hearing. You and your doctor will decide if you can continue treatment or if you need to take another type of antibiotic.
- You may be more prone to joint pain or swelling or tendon damage if you are aged over 60 years, your kidneys do not work well or you have received organ transplantation.
- Speak with your doctor if you are taking a corticosteroid (medicines such as hydrocortisone and prednisolone) or need to have treatment with a corticosteroid. You may be especially prone to tendon damage if you are taking a corticosteroid and a fluoroquinolone medicine at the same time.
- You should not take a fluoroquinolone medicine if you have ever had a serious side effect with a fluoroquinolone or a quinolone medicine and you should speak with your doctor immediately.
- If you have any questions or concerns about your medicines, speak to your doctor or

pharmacist.

Information for healthcare professionals

- Fluoroquinolones are associated with prolonged (up to months or years), serious, disabling and potentially irreversible drug reactions affecting several, sometimes multiple, systems, organ classes and senses.
- The serious side effects include tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impaired hearing, vision, taste and smell.
- Tendon damage (especially to Achilles tendon but also other tendons) can occur within 48 hours of starting fluoroquinolone treatment but the damage may be delayed several months after stopping treatment.
- Patients who are older, have renal impairment or have had solid organ transplantation and those being treated with a corticosteroid are at higher risk of tendon damage. Concomitant treatment with a fluoroquinolone and a corticosteroid should be avoided.
- Fluoroquinolone treatment should be discontinued at the first sign of tendon pain or inflammation and patients should be advised to stop treatment with a fluoroquinolone and speak with the doctor in case of symptoms of neuropathy such as pain, burning, tingling, numbness or weakness so as to prevent development of potentially irreversible condition.
- Fluoroquinolones should generally not be used in patients who have had serious adverse reactions associated with the use of quinolone or fluoroquinolone medicines.
- Up-to-date summary of product characteristics should be consulted for authorized indications when considering treatment with a fluoroquinolone medicine. This is because the indications for these medicines have been restricted.
- The benefits and risks of fluoroquinolones will be monitored continuously and a drug utilization study will evaluate the effectiveness of the new measures to reduce inappropriate use of fluoroquinolones by investigating changes in prescribing behaviour.

Fluoroquinolones and quinolones are a class of broad-spectrum antibiotics that are active against bacteria of both Gram-negative and Gram-positive classes. Fluoroquinolones are of value in certain infections, including some life-threatening ones, where alternative antibiotics are not sufficiently effective.

The review covered medicines containing the following fluoroquinolone and quinolone antibiotics: cinoxacin, ciprofloxacin, flumequine, levofloxacin, lomefloxacin, moxifloxacin, nalidixic acid, norfloxacin, ofloxacin, pefloxacin, pipemidic acid, prulifloxacin and rufloxacin.

The review concerned only medicines given systemically (by mouth or injection) and inhaled medicines. The CHMP opinion will be forwarded to the European Commission, which will issue a final legally binding decision applicable in all EU countries. In Europe, national authorities will enforce this decision for the fluoroquinolone and quinolone medicines and they will also take other appropriate measures to promote the correct use of these antibiotics.

In Hong Kong, there are 190 registered pharmaceutical products for systemic administration containing fluoroquinolones and quinolones, including ciprofloxacin (81 products), levofloxacin (62 products), moxifloxacin (6 products), norfloxacin (7 products), ofloxacin (30 products), sparfloxacin (1 product), prulifloxacin (1 product), nalidixic acid (1 product) and pipemidic acid (1 product). All products are prescription-only medicines.

Related news was previously issued by overseas drug regulatory authorities and was reported in the Drug News Issue No. 46, 79, 81, 87, 88 and 108. The DH issued letters to inform local healthcare professionals on the warnings on 16 August 2013, 13 May 2016 and 8 October 2018. In 2013, the Registration Committee discussed the safety of fluoroquinolones with peripheral neuropathy, and decided that the relevant warnings should be included in the sales packs and/or package inserts of the products. In 2016, the Registration Committee further discussed the safety of fluoroquinolones with disabling and potentially permanent side effects of the tendons, muscles,

joints, nerves, and central nervous system, and subsequently decided to remain vigilant on further updates by other overseas drug regulatory authorities.

As of 5 December 2018, the DH has received 4 cases of ADR related to levofloxacin and 1 case related to moxifloxacin; and of these 5 cases, one case (of the levofloxacin) was related to tendinitis and neuropathy, while the other 4 cases were not related to adverse effects mentioned in the EMA's announcement. The DH has not received any case of ADR related to other fluoroquinolones and quinolones. In light of the EMA announcement in February 2017, October and November 2018, the matter will be further discussed by the Registration Committee. The DH will maintain vigilant on any further update from these health authorities for consideration of any action deemed necessary.

EU: Valsartan from Mylan laboratories in India can no longer be used in EU medicines due to NDEA impurity

On 19 November 2018, the EMA announced that authorities in the EU are taking action after an impurity, *N*-nitrosodiethylamine (NDEA), was found in some batches of valsartan made by Mylan Laboratories Limited in Hyderabad, India.

European Directorate for the Quality of Medicines and Healthcare (EDQM) has now suspended the manufacturer's certificate of suitability to the monographs of the European Pharmacopoeia (CEP) (a certificate of compliance with European standards for quality testing), effectively prohibiting the use of its valsartan in EU medicines.

In addition, national authorities in the EU have started recalling affected batches of medicines containing Mylan's valsartan and are conducting further tests to determine the extent of the contamination.

NDEA and the related compound *N*-nitrosodimethylamine (NDMA), which have been seen in 'sartans' from other manufacturers, are classified as probable human carcinogens (substances that could cause cancer). As with previous findings of NDEA and NDMA, there is no immediate risk to patients. It is riskier for patients to suddenly stop taking high blood pressure medication. Patients should therefore not stop any treatments without consulting their doctor or pharmacist.

The presence of impurities in valsartan medicines and other sartans is thought to be linked to the synthesis of a specific ring structure (tetrazole) which is present in some sartan medicines. The EMA's review of sartans with this structure is continuing and the Agency is working closely with national authorities, international partners and the EDQM. Companies marketing sartan medicines in the EU have been asked to test their products for these impurities. Additional testing is being carried out by EU laboratories. The EMA will update the public as soon as new information becomes available. The EMA is also working with manufacturers to determine what measures can be taken to reduce or eliminate the impurities from future batches of their products.

In Hong Kong, as of 5 December 2018, there are 253 registered pharmaceutical products containing valsartan (83 products), candesartan (19 products), irbesartan (64 products), losartan (70 products) and olmesartan (17 products). All products are prescription-only medicines.

Regarding impurities in valsartan, a public announcement was issued on 6 July 2018, and the DH issued letters to inform local healthcare professionals on 6 July 2018, 9 July 2018, 25 July 2018 and 3 August 2018. Related news for the detection of impurities in sartan-containing products was also previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 105, 106, 107 and 108.

In summary, there are four manufacturers, namely Zhejiang Huahai, Zhejiang Tianyu and Zhuhai Rundu in China and Hetero Labs Limited in India, reported to have detection of trace amounts of NDMA in the valsartan Active Pharmaceutical Ingredient (API) by various overseas drug regulatory authorities. The DH contacted the certificate holders of all registered valsartan products to follow up on the local impact regarding valsartan API produced by the above mentioned

manufacturers.

For API produced by Zhejiang Huahai, there are 5 affected products (HK-61786, HK-61787, HK-61784, HK-61785 and HK-60794) marketed in Hong Kong. The DH instructed the certificate holders to recall all the products from the market as a precautionary measure on 6 July 2018, and the DH noted that all the recalls have been completed.

For API produced by Zhejiang Tianyu, amongst the registered pharmaceutical products containing valsartan, there is only one product namely Retoni Tablets 80mg (HK-65604) registered by Swiss Pharmaceutical Co. Limited (Swiss Pharmaceutical) which has used API produced by Zhejiang Tianyu and is available in the local market. As confirmed with Swiss Pharmaceutical, the API was tested by the Taiwan Food and Drug Administration (TFDA) and the company has not received any notice from the TFDA for NDMA contamination. The DH collected samples of Retoni tablets for analysis and no NDMA was detected.

For API produced by Zhuhai Rundu and Hetero Labs Limited, the certificate holders confirmed that the valsartan products available in local market are not manufactured using API produced by Zhuhai Rundu or Hetero Labs Limited.

Regarding the announcements issued by various overseas drug regulatory authorities on the detection of the second impurity of NDEA in the valsartan API produced by Zhejiang Huahai, there should be no local impact as all valsartan products manufactured using API produced by Zhejiang Huahai have been recalled from the market.

In light of the above EMA's announcement, and announcements issued by various overseas drug regulatory authorities on the detection of NDEA in the valsartan API produced by Mylan Laboratories Limited in India, the certificate holders confirmed that the valsartan products available in local market are not manufactured using API produced by this company.

Regarding the EMA's announcement on the detection of NDEA in losartan in the API produced by Hetero Labs Limited, the United States (US) Food and Drug Administration (FDA)'s announcement on NDEA in the losartan API produced by Zhejiang Huahai, and the announcements issued by the EMA, US FDA and TFDA on NDEA in the irbesartan API produced by Aurobindo Pharma in India, the DH has contacted the certificate holders of all registered candesartan, irbesartan, losartan and olmesartan products and will continue to follow up on the impact of NDEA impurities on the products available in the local market.

As of 5 December 2018, the DH has received 15 cases of ADR related to valsartan, candesartan, irbesartan, losartan and olmesartan. None of them are concluded to be related to the presence of NDMA and/or NDEA. The DH will keep vigilant on any further updates on the matter issued by overseas regulatory authorities.

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.

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 impurities NDMA and NDEA in sartan-containing (candesartan, irbesartan, losartan, olmesartan and valsartan) products.

US: FDA warns about severe worsening of multiple sclerosis after stopping the medicine Gilenya (fingolimod)

On 20 November 2018, the US FDA warned that when the multiple sclerosis (MS) medicine Gilenya (fingolimod) is stopped, the disease can become much worse than before the medicine was started or while it was being taken. This MS worsening is rare but can result in permanent disability. As a result, FDA has added a new warning about this risk to the prescribing information of the Gilenya drug label and patient medication guide.

Healthcare professionals should inform patients before starting treatment about the potential risk of severe increase in disability after stopping Gilenya. When Gilenya is stopped, patients should be

carefully observed for evidence of an exacerbation of their MS and treated appropriately. Patients should be advised to seek immediate medical attention if they experience new or worsened symptoms of MS after Gilenya is stopped. These symptoms vary and include new or worsened weakness, increased trouble using arms or legs, or changes in thinking, eyesight or balance. Gilenya treatment may have to be stopped for reasons such as ADRs, planned or unplanned pregnancy, or because the medicine is not working. However, patients should not stop taking it without first talking to their prescribers, as stopping treatment can lead to worsening MS symptoms.

In the 8 years since Gilenya was approved in September 2010, FDA identified 35 cases of severely increased disability accompanied by the presence of multiple new lesions on magnetic resonance imaging (MRI) that occurred 2 to 24 weeks after Gilenya was stopped. Most patients experienced this worsening in the first 12 weeks after stopping. FDA analyses include only reports submitted to FDA and those found in the medical literature, so there may be additional cases about which FDA is unaware. The severe increase in disability in these patients was more severe than typical MS relapses, and in cases where baseline disability was known, appeared unrelated to the patients' prior disease state. Several patients who were able to walk without assistance prior to discontinuing Gilenya progressed to needing wheelchairs or becoming totally bedbound. In patients experiencing worsening of disability after stopping Gilenya, recovery varied. Seventeen patients had partial recovery, 8 experienced permanent disability or no recovery, and 6 eventually returned to the level of disability they had before or during Gilenya treatment.

In Hong Kong, Gilenya Hard Capsules 0.5mg (HK-61192) is a pharmaceutical product registered by Novartis Pharmaceuticals (HK) Limited, and is a prescription-only medicine. As of 5 December 2018, the DH has received 3 cases of ADR related to fingolimod, but these cases are not related to worsening of MS after stopping the drug. In light of the above FDA's announcement, the DH issued a letter to inform local healthcare professionals to draw their attention on 21 November 2018 and the matter will be discussed by the Registration Committee.

US: Fresenius Kabi issues voluntary nationwide recall of Sodium Chloride Injection, USP, 0.9% due to product labeling incorrectly stating stoppers do not contain latex

On 20 November 2018, the US FDA announced that Fresenius Kabi USA is voluntarily recalling 164 lots of Sodium Chloride Injection, USP, 0.9%, 10mL fill in a 10mL vial and Sodium Chloride Injection, USP, 0.9%, 20mL fill in a 20mL vial to the user level. The product insert states that stoppers for both the 10mL and the 20mL vials do not contain natural rubber latex; the tray label for the two vial sizes and the vial label for the 20mL vial also state that the stoppers do not contain latex. The product is being recalled because the stoppers contain natural rubber latex. Please refer to the tables below for a full list of the affected lots including lot numbers and expiration dates.

Sodium Chloride Injection, USP, 0.9%, 10 mL fill in a 10 mL vial (Unit of Sale NDC Number: 63323-186-10; Unit of Use NDC Number: 63323-186-01; Product Code: 918610)

Batch Number	Expiration Date
6013112, 6013113, 6013114, 6013180, 6013181, 6013182	11/2018
6013237, 6013238, 6013239	01/2019
6013468, 6013512, 6013513, 6013551, 6013552, 6013553, 6013607, 6013608, 6013610	02/2019
6013627, 6013678, 6013679, 6013822, 6013823, 6013824	03/2019
6013924, 6013925, 6013926	04/2019
6014003, 6014004, 6014005, 6014260, 6014301, 6014302	05/2019
6014303, 6014304, 6014305, 6014306, 6014307, 6014384, 6014404, 6014405, 6014453, 6014454, 6014455, 6014479	06/2019
6014557, 6014558, 6014606	07/2019
6014649, 6014650, 6014704, 6014766, 6014767, 6014768, 6014841, 6014842, 6014843, 6014861, 6014862, 6014863	08/2019
6015049, 6015050, 6015088	09/2019
6015118, 6015127, 6015128, 6015186, 6015187, 6015188, 6015233, 6015234, 6015235	10/2019

6015285, 6015286, 6015287, 6015408, 6015409, 6015410, 6015452, 6015453, 6015454, 6015572	11/2019
6015573, 6015574, 6015616, 6015617, 6015618	12/2019
6015922, 6015923, 6015924	01/2020
6016002, 6016003, 6016004, 6016077, 6016104, 6016208, 6016209, 6016210, 6016258, 6016259, 6016260, 6016261	02/2020
6016262, 6016263, 6016264, 6016323, 6016324, 6016325, 6016383, 6016384, 6016385, 6016386, 6016387, 6016388, 6016389	03/2020
6016584, 6016585, 6016621, 6016622, 6016623	04/2020
6016765, 6016766, 6016767, 6016768, 6016769	05/2020
6016875, 6016876, 6016877, 6016878, 6016879, 6017288, 6017289, 6017290, 6017291	06/2020
6017382, 6017425, 6017426, 6017427, 6017428, 6017429, 6017470, 6017471, 6017472, 6017473, 6017474	07/2020
6017675, 6017725, 6017726	08/2020

Sodium Chloride Injection, USP, 0.9%, 20 mL fill in a 20 mL vial (Unit of Sale NDC Number: 63323-186-20; Unit of Use NDC Number: 63323-186-03; Product Code: 918620)

Batch Number	Expiration Date
6013062	11/2018
6014162, 6014163, 6014164	05/2019
6014377, 6014378, 6014379	06/2019
6016005, 6016071, 6016072, 6016073	02/2020
6017383, 6017384, 6017422, 6017423, 6017424	07/2020

For the population most at risk, those with a severe allergic reaction to latex, there is probability of an anaphylactic reaction, and this could result in hospitalization or death. As of 20 November 2018, Fresenius Kabi USA has not received any reports of adverse events related to this recall.

Sodium Chloride Injection, USP, 0.9% is indicated for diluting or dissolving drugs for intramuscular, intravenous or subcutaneous injection according to instructions of the manufacturer of the drug to be administered. It is also indicated for use in flushing of intravenous catheters. The product is packaged as Sodium Chloride Injection, USP, 0.9%, 10mL fill in a 10mL vial; Sodium Chloride Injection, USP, 0.9%, 20mL fill in a 20mL vial; both size vials are packaged in a 25-unit tray.

In Hong Kong, Sodium Chloride for Intravenous Infusion 0.9% w/v (HK-62156) is a pharmaceutical product registered by Fresenius Kabi Hong Kong Limited (Fresenius Kabi), and is a prescription-only medicine. As confirmed with Fresenius Kabi, the pack sizes of 10ml and 20ml are not registered in Hong Kong.

On 26 November 2018, the DH endorsed a licensed drug wholesaler, namely Vantone Medical Supplies Co. Ltd. (Vantone) to recall one batch of Sodium Chloride Injection USP 0.9% 10ml (batch number: 6016259) from the market because of a potential quality issue.

The DH received notification from Vantone that the manufacturer of the above product in the US had informed Vantone to recall one batch (6016259) of the product from the market due to a statement labeling incorrectly stating stoppers do not contain latex on the product insert for the above batch. According to Vantone, 100 vials of the affected batch were imported and supplied to one private doctor for the treatment of particular patients. Vantone had informed the private doctor about the recall. The products of the affected batch has been returned to Vantone.

As of 5 December 2018, the DH has not received any case of ADR in connection with the above batch of the product. The product, Sodium Chloride Injection USP 0.9% 10ml is indicated for diluting or dissolving drugs for injections, is not a registered pharmaceutical product in Hong Kong. A notice was posted on the Drug Office website on 26 November 2018 to alert the public of the product recall.

US: FDA warns about rare but serious risks of stroke and blood vessel wall tears with multiple sclerosis drug Lemtrada (alemtuzumab)

On 29 November 2018, the US FDA warned that rare but serious cases of stroke and tears in the lining of arteries in the head and neck have occurred in patients with MS shortly after they

received Lemtrada (alemtuzumab). These problems can lead to permanent disability and even death. As a result, FDA has added a new warning about these risks to the prescribing information in the drug label and to the patient medication guide. FDA has also added the risk of stroke to the existing *Boxed Warning*, FDA's most prominent warning.

Alemtuzumab is also approved under the brand name Campath, which was approved in May 2001 to treat a type of cancer called B-cell chronic lymphocytic leukemia (B-CLL). The Campath drug label will also be updated to include these risks in the *Adverse Reactions* section under *Postmarketing Experience*.

Patients or their caregivers should seek emergency treatment as soon as possible if the patient experiences signs or symptoms of a stroke or tears in the lining of the head and neck arteries, called arterial dissection, which can include:

- Sudden numbness or weakness in the face, arms, or legs, especially if it occurs on only one side of the body.
- Sudden confusion, trouble speaking, or difficulty understanding speech.
- Sudden trouble seeing in one or both eyes.
- Sudden trouble with walking, dizziness, or loss of balance or coordination.
- Sudden severe headache or neck pain.

Most patients taking Lemtrada who developed stroke or tears in the artery linings, developed symptoms within 1 day of receiving Lemtrada. One patient reported symptoms that occurred 3 days after treatment.

Healthcare professionals should advise patients at every Lemtrada infusion to seek immediate emergency medical attention if they experience symptoms of ischemic or hemorrhagic stroke or cervicocephalic arterial dissection. The diagnosis is often complicated because early symptoms such as headache and neck pain are not specific. Promptly evaluate patients who complain of symptoms consistent with these conditions.

In the nearly five years since FDA approved Lemtrada in 2014 to treat relapsing forms of MS, FDA identified 13 worldwide cases of ischemic and hemorrhagic stroke or arterial dissection that occurred shortly after the patient received Lemtrada. This number includes only reports submitted to FDA, so additional cases FDA is unaware of may have occurred. Twelve of these cases reported symptoms within 1 day of receiving Lemtrada.

In Hong Kong, Lemtrada Concentrate for Solution for Infusion 12mg/1.2ml (HK-64543) is a registered pharmaceutical product containing alemtuzumab. The product is registered by Sanofi-Aventis Hong Kong Limited, and is a prescription-only medicine. As of 5 December 2018, the DH has not received any case of ADR related to alemtuzumab. In light of the above FDA's announcement, the DH issued a letter to inform local healthcare professionals to draw their attention on 30 November 2018 and the matter will be discussed by the Registration Committee.

Drug Recall

DH endorsed recall of Ipufen Tablets 200mg (HK-64033)

On 8 November 2018, the DH endorsed a licensed drug wholesaler, Hitpharm Pharmaceutical Company Ltd. (Hitpharm), to recall all batches of Ipufen Tablets 200mg (HK-64033) from the market due to a quality issue.

During the DH's market surveillance, samples of the above pharmaceutical product were collected for analysis. Testing results from the Government Laboratory showed that the samples failed the disintegration test, which might affect the efficacy of the product.

Hitpharm thus voluntarily recalled the product from the market. The DH has also instructed Hitpharm to report the root cause upon investigation by its manufacturer in Taiwan.

According to Hitpharm, the product has been supplied to local private doctors and pharmacies.

The above pharmaceutical product contains Ibuprofen, which is a Part 1 poison under the Pharmacy and Poisons Ordinance (Cap. 138) and is used to treat pain and inflammation. It can only be supplied at a pharmacy under the supervision of a registered pharmacist.

As of 5 December 2018, the DH has not received any case of ADR in connection with the above product. Press release was posted on the Drug Office website on 8 November 2018 to alert the public of the product recall.

Drug Incident

Woman arrested for suspected illegal sale of unregistered pharmaceutical products

On 12 November 2018, the DH conducted an operation against the sale of unregistered pharmaceutical products labelled in Japanese, during which a 31-year-old woman was arrested for suspected illegal sale of unregistered pharmaceutical products and Part 1 poisons.

Acting upon a public complaint, unregistered pharmaceutical products labelled in Japanese were found being offered for sale via a social media platform. Two products that did not bear Hong Kong pharmaceutical product registration numbers were seized during the operation.

One of the products is a cold and flu medication labelled in Japanese. It is believed to contain tranexamic acid, dihydrocodeine and methylephedrine, which are all Part 1 poisons under the Pharmacy and Poisons Ordinance (Cap. 138). Tranexamic acid is used in the treatment of haemorrhage and can cause gastrointestinal disturbances, and inappropriate use may cause cerebral thrombosis. Dihydrocodeine is an opioid analgesic used as a cough suppressant and for pain relief, and its side effects include nausea, vomiting, constipation and drowsiness. Methylephedrine is used for nasal congestion and cough, and it may cause tachycardia, anxiety, restlessness and insomnia.

The other product is named Eve Quick DX and is believed to contain the Part 1 poison ibuprofen. Ibuprofen is a non-steroidal anti-inflammatory drug for pain relief with side effects including gastrointestinal bleeding.

People who have purchased the above products should stop using them and consult healthcare professionals for advice if they are feeling unwell. Press release was posted on the Drug Office website on 12 November 2018 to alert the public of the drug incident.

Dispatch arrangements of quadrivalent seasonal influenza vaccines

On 27 November 2018, the DH was informed by a licensed drug wholesaler, Sanofi-Aventis Hong Kong Limited (Sanofi), that it has decided to take a precautionary measure to suspend the market supply of a batch of quadrivalent seasonal influenza vaccines (SIVs) (box label: R3J721V; syringe label: R3J72) and arrange to dispatch a new batch of

quadrivalent SIVs to local private healthcare facilities as soon as possible.

According to the information provided by Sanofi, around 175 000 doses of the affected batch of SIVs have been imported to Hong Kong and part of the batch has been distributed to the DH, the Hospital Authority (HA) and healthcare facilities. Based on the DH's preliminary statistics, there are around 100 000 doses of unused vaccines in Hong Kong. Sanofi has committed to contact relevant organisations and arrange to dispatch a new batch of vaccines as soon as possible.

The DH has immediately suspended the use of the affected vaccines. The DH's services, including the Elderly Health Centres, suspended seasonal influenza vaccination service until the supplier dispatched a new batch of SIVs. On the other hand, the School Outreach Vaccination Pilot Programme under the DH is not affected by the incident as SIVs used under the pilot programme are supplied by another company. On 3 December 2018, the DH announced that clinics under the DH and the HA have fully resumed vaccination service of SIVs. Stocks at public clinics have all been replenished with other unaffected batches of influenza vaccines.

The DH also reminded residential care home operators and visiting doctors to pay attention on whether they have procured the affected quadrivalent SIVs. If they have, they should suspend the use of such vaccines and contact Sanofi for relevant arrangements.

As of 5 December 2018, number of Guillian-Barré Syndrome (within the period of 5 days and 6 weeks after vaccination) and other serious neurological adverse events reported among vaccinated persons in the 2018/19 season were zero. Members of the public are advised to consult healthcare professionals if they feel unwell after receiving seasonal influenza vaccination.

According to Sanofi, samples of the concerned batch of quadrivalent SIVs were found to contain white particles by Taiwan authority. The company said that it has not received any report regarding the presence of white particles in the same batch of SIVs currently supplied to Hong Kong.

The DH has requested Sanofi to submit a full investigation report regarding the presence of white particles in the affected batch of SIVs. The DH has also asked Sanofi and another supplier providing quadrivalent SIVs to Hong Kong to import additional quantities of vaccines to meet the local demand.

Press releases were posted on the Drug Office and the DH websites on 27 November 2018 and on the DH website on 29 November 2018 and 3 December 2018 to alert the public of the drug incident.

DH urged public not to buy or use facial mask with controlled substance fluocinolone acetonide

On 30 November 2018, the DH appealed to the public not to buy or use a facial mask, namely Skin 18, which was found to contain an undeclared and controlled substance.

Acting upon a public complaint, the DH found that the above facial mask has been offered for sale at a retail shop in Mong Kok. Samples of the product were collected for analysis and test results from the Government Laboratory revealed that the samples contained fluocinolone acetonide, a Part 1 poison under the Pharmacy and Poisons Ordinance (Cap. 138).

Fluocinolone acetonide is a steroid substance. Products containing fluocinolone acetonide should only be sold at pharmacies under the supervision of registered pharmacists upon a doctor's prescription. Inappropriate or excessive application of steroids could cause skin problems and body-wide side effects like moon face, high blood pressure, high blood sugar, muscle atrophy, adrenal insufficiency and even osteoporosis.

Press release was posted on the Drug Office website on 30 November 2018 to alert the public of the drug incident.

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

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.

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.