Drug News
藥 物 情 報

Issue Number 121

This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in November 2019 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: Kyprolis (carfilzomib) and risk of progressive multifocal leukoencephalopathy and Hepatitis B virus reactivation

On 4 November 2019, the Health Sciences Authority (HSA) of Singapore announced that Amgen Biotechnology Singapore informed healthcare professionals of the risk of progressive multifocal leukoencephalopathy (PML), a rare, often rapidly progressive demyelinating disease of the central nervous system, and Hepatitis B virus (HBV) reactivation associated with the use of Kyprolis (carfilzomib).

Healthcare professionals are advised to monitor patients for any new or worsening neurologic, cognitive or behavioural signs and symptoms that may be suggestive of PML as part of the differential diagnosis of central nervous system disorders. If PML is suspected, patients should be referred to a specialist and appropriate diagnostic testing should be initiated. It is advisable to discontinue Kyprolis if PML diagnosis is confirmed. Healthcare professionals are also advised to test patients for HBV infection before initiating treatment with Kyprolis. For patients who are carriers of HBV, prophylaxis with antivirals should be considered. Carriers of HBV who require treatment with Kyprolis should be closely monitored for signs and symptoms of active HBV infection throughout and following the end of treatment.

In Hong Kong, there are 2 registered pharmaceutical products containing carfilzomib, namely Kyprolis for Injection 60mg/vial (HK-64828) and Kyprolis for Injection 30mg/vial (HK-65431). Both products are registered by Amgen Hong Kong Limited, and are prescription-only medicines. As on 5 December 2019, the Department of Health (DH) has received 16 cases of adverse drug reaction (ADR) related to carfilzomib, but these cases are not related to PML or HBV reactivation.

In light of the above HSA's announcement, the DH issued a letter to inform local healthcare professionals to draw their attention on 5 November 2019. Related news on the risk of reactivation of hepatitis B virus by carfilzomib was issued by the Medicines and Healthcare products Regulatory Agency (MHRA). The risk of reactivation of hepatitis B virus will be discussed by the Registration Committee of the Pharmacy and Poisons Board (Registration Committee). The DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

EU: Measures to minimise risk of serious side effects of multiple sclerosis medicine Lemtrada

On 15 November 2019, the European Medicines Agency (EMA) of European Union (EU) recommended restriction of the use of the multiple sclerosis medicine Lemtrada (alemtuzumab) due to reports of rare but serious side effects, including deaths. New measures to identify and manage the serious side effects are also recommended. The side effects include cardiovascular disorders (affecting the heart, circulation and bleeding as well as stroke) and immune-related disorders (caused by the body's defence system not working properly).

Lemtrada should only be used to treat relapsing-remitting multiple sclerosis if the disease is highly active despite treatment with at least one disease-modifying therapy or if the disease is worsening rapidly. Lemtrada must also no longer be used in patients with certain heart, circulation or bleeding disorders or in patients who have autoimmune disorders other than multiple sclerosis.

The medicine should only be given in a hospital with ready access to intensive care facilities and specialists who can manage serious adverse reactions.

The EMA has also recommended updating the physician's guide and the patient information pack with advice on minimising the risk of serious cardiovascular disorders, which may occur shortly after a Lemtrada infusion (drip), and immune-related conditions, which may occur many months and possibly years after the last treatment.

These recommendations were issued by the EMA's safety committee, Pharmacovigilance Risk Assessment Committee (PRAC), and have been endorsed by the EMA's human medicines committee, Committee for Medicinal Products for Human Use (CHMP). They will replace the temporary measures introduced in April 2019 while the review of Lemtrada was under way. The changes come into force when the European Commission issues its decision.

Information for patients

- Serious but rare side effects have been reported with Lemtrada, including disorders of the heart, blood vessels and problems of the immune system which may affect blood and organs such as the lungs and liver.
- Their doctor will review their treatment to check if treatment with Lemtrada remains appropriate.
- They will be watched closely in hospital when they receive Lemtrada and for a short period afterwards, but some side effects can develop days or months later. They must get medical help immediately if:
  - they have any chest pain or breathing difficulty while Lemtrada is being given to them or in the next few days (signs of heart problem);
  - they cough up blood or have breathing difficulty (signs of bleeding in the lungs);
  - they have drooping of the face, severe headache, neck pain, weakness on one side or difficulty speaking (signs of stroke or damage to blood vessels in their brain);
  - their skin or eyes turn yellow, or they have dark urine, pain in their belly or they bleed or bruise easily (signs of liver damage);
  - they have fever, swollen glands, bruising or rash (signs of a dangerous immune disorder called haemophagocytic lymphohistiocytosis).
- Carefully read the updated Lemtrada patient guide and patient alert card because they contain important information and reminders about what to watch out for.
- Speak with their doctor or pharmacist if they have any questions or concerns about their treatment.

Information for healthcare professionals

- Rare but serious effects that can occur within 1 to 3 days of Lemtrada infusion include myocardial ischaemia, myocardial infarction, cerebral haemorrhage, cervicocephalic arterial dissection, pulmonary alveolar haemorrhage and thrombocytopenia.
- Autoimmune side effects occurring within 48 months or longer after the last dose of Lemtrada include autoimmune hepatitis and haemophilia A as well as immune thrombocytopenic purpura, thyroid disorders and, rarely, nephropathies. Haemophagocytic lymphohistiocytosis, a syndrome of immune activation characterised by fever, hepatomegaly and cytopenia, has also been reported.
- Serious infections as well as reactivation of Epstein-Barr virus can also occur.
- Lemtrada should now only be used as a single disease-modifying therapy in adults with relapsing- remitting multiple sclerosis with:
  - highly active disease despite a full and adequate course of treatment with at least one disease-modifying therapy or
  - rapidly evolving severe disease defined by 2 or more disabling relapses in one year, and with 1 or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared to a recent MRI.
- In addition to current contraindications, Lemtrada is now also contraindicated in:
  - severe active infections until complete resolution
  - uncontrolled hypertension
  - history of angina pectoris, myocardial infarction, stroke or dissection of the cervicocephalic arteries
  - coagulopathy, on antiplatelet or on anti-coagulant therapy
  - concomitant autoimmune diseases other than multiple sclerosis
- Patients should receive Lemtrada only in a hospital with ready access to intensive care and with specialists and equipment for diagnosing and managing cardiac and

cerebrovascular reactions and cytokine release syndrome, as well as autoimmune disorders and infections.
- The summary of product characteristics includes updated information on monitoring for side effects, including instructions on evaluations before, during and after Lemtrada infusion.
- The guide for healthcare professionals will also be updated.
- The patient should be provided with the Lemtrada patient guide and patient alert card and be advised to seek medical help immediately if any signs of serious side effects occur.

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 on 5 December 2019, the DH has received 3 cases of ADR related to alemtuzumab, but these cases are not related to immune-mediated conditions such as autoimmune hepatitis and haemophagocytic lymphohistiocytosis, or serious cardiovascular reactions.

Related news was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 109, 114 and 120. The DH issued letters to inform local healthcare professionals to draw their attention on 30 November 2018 and 15 April 2019.

In September 2019, the Registration Committee discussed the matter, and decided that the sales pack or package insert of the product should include safety information about immune-mediated conditions and problems with the heart and blood vessels. The DH will remain vigilant on safety update of the product issued by other overseas drug regulatory authorities.

EU: Xeljanz to be used with caution for all patients at high risk of blood clots

On 15 November 2019, the EMA has concluded that Xeljanz (tofacitinib) could increase the risk of blood clots in the lungs and in deep veins in patients who are already at high risk.

As a result, the EMA is recommending that Xeljanz should be used with caution in all patients at high risk of blood clots. In addition, the maintenance doses of 10 mg twice daily should not be used in patients with ulcerative colitis who are at high risk of blood clots unless there is no suitable alternative treatment. Further, the EMA is recommending that, due to an increased risk of infections, patients older than 65 years of age should be treated with Xeljanz only when there is no alternative treatment.

These recommendations follow the EMA's review of an ongoing study (study A3921133) in patients with rheumatoid arthritis and an increased risk of cardiovascular disease, plus data from earlier studies and consultation with experts in the field. All data combined showed that the risk of blood clots in deep veins and lungs was higher in patients taking Xeljanz, especially the 10 mg twice daily dose, and in those being treated for an extended period. Results also showed a further increased risk of serious and fatal infections in patients older than 65 years of age.

The recommendations were issued by the PRAC and have been endorsed by the CHMP. They will replace the measures put in place at the start of the review in May 2019. The changes come into force when the European Commission issues its decision.

Information for patients
- Xeljanz could increase the risk of blood clots in patients who are already at high risk.
- If they are being treated with Xeljanz their doctor will review their risk of blood clots and modify their treatment if necessary.
- They may be at high risk of blood clots in the lungs and in deep veins if they have had a heart attack or have heart failure, cancer, inherited blood clotting disorder or a history of blood clots.
- They may also be at risk if they are taking combined hormonal contraceptives or hormone replacement therapy, will have or have recently had major surgery or are immobilised.
- To evaluate the risk their doctor will also consider their age, whether they are obese (their body mass index (BMI) is above 30), have diabetes, have elevated blood pressure, or smoke.
- If they are at high risk or older than 65 years of age, their doctor may switch their treatment if there is an alternative treatment for them.
- If they are being treated with Xeljanz, they should not change the dose or stop taking the medicine without discussing it with their

doctor.
- Ask for medical attention immediately if they develop sudden shortness of breath or difficulty in breathing, chest pain or pain in their upper back, swelling of the leg or arm, leg pain or tenderness, or redness or discoloration in the leg or arm. These may be symptoms of a blood clot in their lungs or veins.
- If they have any concerns about their medicine, they should discuss them with a healthcare professional.

Information for healthcare professionals
- An EMA review has found a dose-dependent increased risk of serious venous thromboembolism (VTE), including pulmonary embolism (PE) (some cases of which were fatal) and deep vein thrombosis in patients taking tofacitinib.
- The review considered data from study A3921133, an ongoing open-label clinical trial evaluating the safety of tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily compared with a tumour necrosis factor (TNF) inhibitor in patients with rheumatoid arthritis. Patients in the study are 50 years of age or older with at least one additional cardiovascular risk factor. After the interim results became available, treatment with tofacitinib 10 mg twice daily was stopped and patients were switched to 5 mg twice daily because of a signal of PE and all-cause mortality. The review also considered additional data from earlier studies.
- The review of study A3921133 showed that compared to treatment with a TNF inhibitor, tofacitinib 5 mg twice daily increased the risk of PE about 3-fold while tofacitinib 10 mg twice daily increased the risk roughly 6-fold.
- In total there were 17 cases of PE out of 3,123 patient-years with the tofacitinib 10 mg twice daily dose and 9 cases of PE out of 3,317 patient-years with the tofacitinib 5 mg twice daily dose compared with 3 cases out of 3,319 patient-years with a TNF inhibitor. Additionally, there were 28 deaths from all causes out of 3140 patient-years in the tofacitinib 10 mg twice daily arm and 19 deaths from all causes out of 3,324 patient-years in the tofacitinib 5 mg twice daily arm compared with 9 cases out of 3323 patient-years in the TNF inhibitor arm.
- As a result, tofacitinib should be used with caution in patients with known risk factors for VTE, regardless of indication and dosage. This includes patients who have had a heart attack or have heart failure, cancer, inherited blood clotting disorders or a history of blood clots, as well as patients taking combined hormonal contraceptives or hormone replacement therapy, are undergoing major surgery or are immobile.
- Other risk factors to be considered when prescribing tofacitinib include age, diabetes, obesity (BMI>30), smoking status and hypertension.
- The use of tofacitinib 10 mg twice daily for maintenance treatment in patients with ulcerative colitis who have known VTE risk factors is not recommended, unless there is no suitable alternative treatment available.
- For treatment of rheumatoid arthritis and psoriatic arthritis, the recommended dose of 5 mg twice daily should not be exceeded.
- Patients should be informed about the signs and symptoms of VTE before receiving tofacitinib and be advised to seek prompt medical help if they develop these symptoms during treatment.
- Available data also showed that the risk of serious infections and fatal infections was further increased in elderly patients above 65 years of age, as compared to younger patients. Therefore, tofacitinib should only be considered in these patients if no suitable alternative treatment is available.
- A letter will be sent to all healthcare professionals expected to prescribe the medicine to inform them of the updated treatment recommendations. The physician's guide and the patient alert card will be updated with advice to minimise the risk of blood clots.

In Hong Kong, Xeljanz Tablets 5mg (HK-63303) and Xeljanz XR Extended Release Tablets 11mg (HK-66141) are registered pharmaceutical products containing tofacitinib. Both products are registered by Pfizer Corporation Hong Kong Limited, and are prescription-only medicines. As on 5 December 2019, the DH has received 5 cases of ADR related to tofacitinib, of which one case is related to deep vein thrombosis.

Related news was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No.112, 115, 117 and 120. The DH issued a letter to inform local healthcare professionals to draw their attention on

29 July 2019. The matter has been discussed by the Registration Committee on 4 December 2019 and decided that the sales pack labels and/or package inserts of registered pharmaceutical products containing tofacitinib should include safety information about increased risk of blood clots and death with higher dose (10 mg twice daily).

UK: Yellow fever vaccine: stronger precautions in people with weakened immunity and in those aged 60 years or older

On 21 November 2019, the MHRA of the United Kingdom (UK) announced that the Commission on Human Medicines has issued a series of recommendations to strengthen measures to minimise risk with the yellow fever vaccine (Stamaril) following very rare fatal reactions. Key recommendations include new and updated contraindications and strengthened precautions to protect those with a weakened immune systems (including for people aged 60 years or older) and standardised risk-benefit evaluation procedures across UK yellow fever vaccination centres to ensure that people only receive the vaccine after a thorough risk assessment.

Two risks unique to yellow fever vaccine are viscerotropic disease (YEL-AVD) and neurotropic disease (YEL-AND), which both resemble yellow fever infection. These are very rare but can be fatal. These risks are more likely to occur in certain groups, particularly people with a weakened immune system, people without a thymus, and people aged 60 years or older. The risks of YEL-AND and YEL-AVD are estimated to be up to 1 per 100,000 primary vaccinees, although this may be up to 4-times greater in those aged 60 years or older.

Cases of YEL-AND have been reported in primary vaccinees with an onset within 30 days of vaccination. The risk appears to be higher in people older than 60 years and younger than 9 months of age (including infants exposed to vaccine through breastfeeding), although cases have been also reported in other age groups. Congenital or acquired immunodeficiency has also been recognised as a potential risk factor. YEL-AND may manifest as high fever with headache that may progress to include 1 or more of confusion, lethargy, encephalitis, encephalopathy, and meningitis. Other neurological signs and symptoms have been reported and include convulsions, Guillain-Barré syndrome, and focal neurological deficits.

Cases of YEL-AVD (formerly described as febrile multiple organ-system failure) have been reported following vaccination with yellow fever vaccine, some of which have been fatal. In most cases reported, the onset of signs and symptoms was within 10 days of vaccination. Initial signs and symptoms of AVD are non-specific and may include pyrexia, myalgia, fatigue, headache and hypotension, potentially progressing quickly to liver dysfunction with jaundice, muscle cytolysis, thrombocytopenia, and acute respiratory and renal failure.

Healthcare professionals are advised:

- Yellow fever vaccine is a highly effective vaccine to protect against life-threatening yellow fever infection; however, strict adherence to contraindications and precautions is essential to reduce the risk of very rare but potentially fatal adverse reactions.
- A letter from the MHRA, Public Health England, National Travel Health Network and Centre, and Health Protection Scotland has been sent to UK yellow fever vaccination centres to inform them of the recommendations and that changes will be made to the product information and standardised pre-vaccination screening tools. Please find below the recommendations listed in the letter:
  - In people aged 60 years or older, due to a higher risk of life-threatening side effects, the vaccine should be given only when there is a significant and unavoidable risk of acquiring yellow fever infection, such as travel to an area where there is a current or periodic risk of yellow fever transmission. This would exclude travel to areas in which vaccination is 'generally not recommended' by World Health Organization (WHO).
  - Only healthcare professionals specifically trained in benefit-risk evaluation of yellow fever vaccine should administer the vaccine, following their individualised assessment of a person's travel itinerary and suitability to receive the vaccine.
  - Do not administer the vaccine to people who have had their thymus gland removed for any reason; who are taking biological drugs that are immunosuppressive or immunomodulating; and who have a first-degree family history of YEL-AVD

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or YEL-AND following vaccination that was not related to a known medical risk factor (i.e. in case of an unidentified genetic predisposition).

- Every vaccinee should be advised to seek emergency medical attention if they develop signs or symptoms of very rare YEL-AND or YEL-AVD and should receive the manufacturer's patient information leaflet as part of the travel consultation.

In Hong Kong, Stamaril Pasteur (Yellow Fever) Vaccine (HK-40600) is registered by Sanofi-Aventis Hong Kong Limited, and is a prescription-only medicine. As on 5 December 2019, the DH has received one case of adverse event following Stamaril vaccination. The case was reported to the DH as a case of yellow fever vaccine-associated viscerotropic disease (YEL-AVD). The case had a few clinical features compatible with YEL-AVD. However, according to the opinion of the World Health Organization (WHO) Yellow Fever Initiative, it cannot be concluded that this case was a definite case of YEL-AVD.

Related news was previously issued by the MHRA and was reported in the Drug News Issue No. 114. In light of the updated contraindications and strengthened precautions in the MHRA's announcement, the DH issued a letter to inform local healthcare professionals to draw their attention on 22 November 2019; and the matter will be discussed by the Registration Committee.

Drug Recall

DH endorsed batch recall of Thiamiject Injection 1000mg ／ 10ml (HK-62703)

On 8 November 2019, the DH endorsed a licensed medicine wholesaler, Sino-Asia Pharmaceutical Supplies Ltd (Sino-Asia), to recall a batch (Batch No.: 7K940; Manufacturing date: 2017-10-11; Expiry date: 2020-10-31) of Thiamiject Injection 1000mg/10ml (HK-62703) from the market due to a potential quality issue.

The DH received notification from Sino-Asia that the stability test of the above-mentioned product indicated that the content of active ingredient was less than the specifications at the end of the 36-month shelf-life. Therefore, the manufacturer decided to shorten the product's shelf-life from 36 months to 24 months. The above-mentioned batch was manufactured in 2017 and therefore has passed the new shelf-life. As a precautionary measure, Sino-Asia is recalling the affected batch from the market.

The above product, containing thiamine, is a prescription medicine used in the prophylaxis and treatment of vitamin B1 deficiency. According to Sino-Asia, the product has been supplied to the DH, the Hospital Authority and private hospitals and some were exported to Macao.

Patients who have used the above product should seek advice from their healthcare professionals if in doubt.

As on 5 December 2019, the DH has not received any case of ADR in connection with the product. A notice was posted on the Drug Office website on 8 November 2019 to alert the public of the product recall.

DH endorsed batch recall of Minocycline HCl for Intravenous Infusion 100mg "Taiyo"

On 15 November 2019, the DH endorsed two licensed drug wholesalers, namely Four Seasons International Limited and Vantone Medical Supplies Co Ltd, to recall one batch (batch number: ES0057) of Minocycline HCl for Intravenous Infusion 100mg "Taiyo" from the market due to a potential quality issue.

The DH received notification from the wholesalers that the manufacturer found a piece of glass in the product of the affected batch during testing, probably due to bottles broken in the production process. As a precautionary measure the manufacturer voluntarily recalls the affected batch of the product.

The aforementioned product, containing minocycline, is a prescription medicine used for the treatment of bacterial infections. The product is not registered in Hong Kong but was imported for the treatment of particular patients by registered medical practitioners. According to the wholesalers, the affected batch has been supplied to the Hospital Authority and private hospitals.

Patients who require use of the above product should seek advice from their attending doctors if

in doubt.

As on 5 December 2019, the DH has not received any case of ADR in connection with the affected product. Press release was posted on the Drug Office website on 15 November 2019 to alert the public of the product recall.

DH endorsed batch recall of Keppra Oral Solution 100mg ／ ml (HK-54926)

On 26 November 2019, the DH endorsed a licensed drug wholesaler, GlaxoSmithKline Ltd (GSK), to recall one batch of Keppra Oral Solution 100mg/ml (HK-54926) from the market because some of the product's label does not match with the registered one.

The DH received notification of GSK that some unregistered French packs of Keppra Oral Solution 100mg/ml (HK-54926) were found to be mixed up in Hong Kong registered packs in a recent shipment of one batch (Lot. No. 1183) of the product. Although the product content is the same, the French packs bear a label different from that of the registered one and renders the product unregistered. Since the supply of unregistered pharmaceutical product contravenes the Pharmacy and Poisons Regulations (Cap. 138A), GSK voluntarily recalls the product from the market.

The above product, containing levetiracetam, is a prescription antiepileptic drug. According to GSK, the product has been supplied to the Hospital Authority, private doctors and a pharmacy.

As on 5 December 2019, the DH has not received any case of ADR related to the affected product. A notice was posted on the Drug Office website on 26 November 2019 to alert the public of the product recall.

DH endorsed recall of six ranitidine-containing products

On 1 November 2019, the DH endorsed a licensed drug wholesaler Welldone Pharmaceuticals Limited (Welldone) to recall six ranitidine-containing products from the market as a precautionary measure due to the potential presence of an impurity in the products. The affected products are Epirant Tab 150mg (HK-56826), Welldone Ranitidine Tab 150mg (HK-57473), Kin Pak Tab 150mg (HK-56824), Wah Tat Tab 150mg (HK-56823), Super Pro Tab 150mg (HK-56825) and Glo-Tac Tab 150mg (HK-57472).

The DH received notification from the products' registration certificate holder Medexrom Limited that the manufacturer is voluntarily recalling the above products because they might contain *N*-nitrosodimethylamine (NDMA). NDMA is classified as a probable human carcinogen based on results from laboratory tests. Because the products are distributed by Welldone in Hong Kong, as a precautionary measure, Welldone is voluntarily recalling the affected products from the market.

The above products are over-the-counter medicines used for the treatment of gastric diseases. According to Welldone, the affected products have been supplied to local pharmacies and medicine companies, and some have been exported to Macao.

As on 5 December 2019, the DH has not received any case of ADR in connection with the products. Press release was posted on the Drug Office website on 1 November 2019 to alert the public of the products recall.

DH endorsed recall of five ranitidine-containing products

On 7 November 2019, the DH endorsed three licensed drug wholesalers, Healthcare Pharmascience Limited (HP), Julius Chen & Co (HK) Limited (JC) and Atlantic Pharmaceutical Limited (Atlantic), to recall five ranitidine-containing products from the market as a precautionary measure due to the presence of an impurity in the products.

The affected products are:

Supplier	Product
HP	Raniplex 150 Tablet 150mg (HK-43456)
JC	Tupast Tablet 150mg (HK-50378) Wontac Tablet 150mg (HK-60085) Jecefarma Ranitidine Tablet 150mg (HK-64041)
Atlantic	Ratic Tablet 150mg (HK-61083)

The DH received information from Macao Health Bureau that Raniplex, Tupast and Wontac were tested and found to contain NDMA. NDMA is a probable human carcinogen based on results from laboratory tests. As a precautionary measure, the suppliers concerned are voluntarily recalling the affected products from the market. In addition, two

other products, i.e. Jecefarma Ranitidine and Ratic, are also being recalled because the raw material ranitidine may contain NDMA.

The above products are over-the-counter medicines used for the treatment of gastric diseases. According to the suppliers, the affected products have been supplied to the local healthcare sector including private doctors, pharmacies, medicine companies, a private hospital and an animal clinic.

As on 5 December 2019, the DH has not received any case of ADR in connection with the products. Press release was posted on the Drug Office website on 7 November 2019 to alert the public of the products recall.

DH endorsed recall of Ulticer Tab 150mg (HK-53488)

On 12 November 2019, the DH endorsed a registration certificate holder, Medreich Far East Limited (Medreich), to recall a ranitidine-containing product, namely Ulticer Tab 150mg (HK-53488), from the market due to the potential presence of an impurity in the product.

The DH received notification from Medreich on 12 November 2019 that the manufacturer suspected that the product might contain the impurity NDMA. NDMA is classified as a probable human carcinogen based on results from laboratory tests. Therefore, as a precautionary measure, Medreich is voluntarily recalling the above product from the market.

The above product is an over-the-counter medicine used for the treatment of gastric diseases. According to Medreich, the product has been supplied to local private doctors and pharmacies.

As on 5 December 2019, the DH has not received any case of ADR in connection with the product. Press release was posted on the Drug Office website on 12 November 2019 to alert the public of the product recall.

DH endorsed recall of two ranitidine-containing products

On 27 November 2019, the DH endorsed two licensed drug suppliers, Cera Medical Limited (Cera) and Sincerity (Asia) Company Limited (Sincerity), to recall two ranitidine-containing products from the market as a precautionary measure due to the presence of an impurity in the products. The affected products are Emtac 150 Tab 150mg (HK-59353) from Cera and Ranitid 150 Tab 150mg (HK-59429) from Sincerity.

In view of the recent recall of ranitidine-containing products, the DH proactively collected samples of similar products from the market for analysis. Test results from the Government Laboratory revealed that the above products contain an impurity of NDMA. NDMA is a probable human carcinogen based on results from laboratory tests. As a precautionary measure, the concerned suppliers are voluntarily recalling the affected products from the market.

The above products are over-the-counter medicines used for the treatment of gastric diseases. According to the suppliers, the affected products have been supplied to local private doctors, pharmacies and medicine companies.

As on 5 December 2019, the DH has not received any case of ADR in connection with the products. Press release was posted on the Drug Office website on 27 November 2019 to alert the public of the products recall.

Overall situation related to detection of NDMA in ranitidine

As on 5 December 2019, there are 67 registered pharmaceutical products containing ranitidine in Hong Kong. These products in the forms of oral preparations and injections are controlled as over-the-counter medicines and prescription-only medicines respectively. As on 5 December 2019, the DH has not received any case of ADR related to ranitidine.

Related news on the detection of NDMA in ranitidine products was previously issued by various overseas drug regulatory authorities. The DH issued a letter to inform local healthcare professionals to draw their attention on 18 September 2019. The DH has contacted the relevant overseas drug regulatory authorities for further information regarding the detection of NDMA in ranitidine products, and continues to remain vigilant on the update findings and investigation result announced by the authorities for consideration of any action deemed necessary.

The DH has contacted the certificate holders of all registered ranitidine products for follow up on the local impact of the issue; and to provide evidence

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that NDMA in the products are below the acceptable limit, and samples of ranitidine-containing products have been collected from the market for analysis. When any health risks are posed to the public, a press statement will be issued as soon as possible. Please find update information at Drug Office's website (www.drugoffice.gov.hk). The following are the main content of the press statements issued previously:

- On 24 September 2019, the DH endorsed a licensed drug wholesaler, GSK, to recall all Zantac products (HK-42792, HK-42793, HK-30459, HK-42045) from the Hong Kong market as a precautionary measure due to the presence of NDMA in the products.
- On 25 September 2019, the DH endorsed licensed drug wholesalers Hind Wing Co Ltd (Hind Wing) and Top Harvest Pharmaceuticals Co Ltd to recall Apo-Ranitidine Tablets (HK-42273, HK-41873) and Zantidon Tablets 150mg (HK-64329) respectively.
- On 27 September 2019, the DH endorsed licensed drug manufacturer APT Pharma Limited and licensed drug wholesaler Eugenpharm International Limited to recall Amratidine Tablets 150mg (HK-53143) and Peptil H 150 Tablets 150mg (HK-65103) respectively.
- On 30 September 2019, the DH endorsed licensed drug wholesaler Vast Resources Pharmaceutical Limited to recall Weidos Tablets 150mg (HK-62210).
- On 11 October 2019, the DH endorsed licensed drug wholesaler Hind Wing to recall Epadoren Solution for Injection 50mg/2ml (HK-61752).
- On 1 November 2019, the DH endorsed licensed drug wholesaler Welldone to recall six ranitidine-containing products: Epirant Tab 150mg (HK-56826), Welldone Ranitidine Tab 150mg (HK-57473), Kin Pak Tab 150mg (HK-56824), Wah Tat Tab 150mg (HK-56823), Super Pro Tab 150mg (HK-56825) and Glo-Tac Tab 150mg (HK-57472).
- On 7 November 2019, the DH endorsed licensed drug wholesalers HP, JC and Atlantic to recall 5 ranitidine-containing products: Raniplex 150 Tablet 150mg (HK-43456), Tupast Tablet 150mg (HK-50378), Wontac Tablet 150mg (HK-60085), Jecefarma Ranitidine Tablet 150mg (HK-64041) and Ratic Tablet 150mg (HK-61083).
- On 12 November 2019, the DH endorsed registration certificate holder Medreich to recall Ulticer Tab 150mg (HK-53488).
- On 27 November 2019, the DH endorsed drug suppliers Cera and Sincerity to recall Emtac 150 Tab 150mg (HK-59353) and Ranitid 150 Tab 150mg (HK-59429) respectively.

The above recalls endorsed by the DH from 24 September 2019 to 11 October 2019 were reported in the Drug News Issue No. 119 and 120. Patients who are taking ranitidine-containing products should not stop taking the medicines, but should seek advice from their healthcare professionals for proper arrangement, e.g. use of alternative medicines with similar uses.

Drug Incident

Public urged not to buy or consume slimming product with undeclared Western drug ingredient sibutramine

On 12 November 2019, the DH appealed to the public not to buy or consume a slimming product named MS Natural Fiber as it was found to contain an undeclared and banned drug ingredient that might be dangerous to health.

During the DH's market surveillance, a sample of the above product was purchased via a social media network platform for analysis. Test results of the Government Laboratory revealed that the sample contained the banned drug ingredient sibutramine.

Sibutramine was once used as an appetite suppressant. Since November 2010, pharmaceutical products containing sibutramine have been banned in Hong Kong because of increased cardiovascular risk.

Members of the public who have purchased the above product should stop consuming it immediately. They should consult healthcare professionals for advice if feeling unwell after consumption.

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.

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The public may visit the website of the Drug Office of the DH for "Health messages on overweight problem and slimming products" and "Information on slimming products with undeclared Western drug ingredients".

Press release was posted on the Drug Office website on 12 November 2019 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 accordance 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: ***Undesirable Medical Advertisements and Adverse Drug Reaction Unit,***
Drug Office, Department of Health,
Suites 2002-05, 20/F, AIA Kowloon Tower,
Landmark East, 100 How Ming Street,
Kwun Tong, Kowloon

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.