Drug News
藥 物 情 報

Issue Number 124

This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in February 2020 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

UK: Class 2 Medicines Recall: Medreich PLC, Ranitidine 150mg Tablets and Ranitidine 300mg Tablets

On 3 February 2020, the Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom (UK) announced that Medreich PLC is recalling all unexpired stock of Ranitidine 150mg Tablets and Ranitidine 300mg Tablets from pharmacies and wholesalers as a precautionary measure due to possible contamination with an impurity *N*-nitrosodimethylamine (NDMA) which has genotoxic and carcinogenic potential.

This is an on-going issue and the MHRA is actively involved with the European Medicines Agency (EMA) and with other medicines regulators to determine any possible impact. An investigation into other potentially impacted products is continuing and further updates will be provided as the investigation progresses.

In Hong Kong, Ulticer Tab 150mg (HK-53488) and Ulticer Tab 300mg (HK-52986; currently not available for sale) are ranitidine products registered by Medreich Far East Limited. On 12 November 2019, the Department of Health (DH) endorsed registration certificate holder Medreich Far East Limited to recall Ulticer Tab 150mg (HK-53488).

As on 5 March 2020, there are 66 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 March 2020, the DH has not received any case of adverse drug reaction (ADR) related to ranitidine.

Related news on the detection of NDMA in ranitidine products was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 122 and 123. 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 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, GlaxoSmithKline Ltd, 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 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 Co Ltd to recall Epadoren Solution for Injection 50mg/2ml (HK-61752).
- On 1 November 2019, the DH endorsed licensed drug wholesaler Welldone Pharmaceuticals Limited 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 Healthcare Pharmascience Limited, Julius Chen & Co (HK) Limited and Atlantic Pharmaceutical Limited to recall five 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 Far East Limited to recall Ulticer Tab 150mg (HK-53488).
- On 27 November 2019, the DH endorsed drug suppliers Cera Medical Limited and Sincerity (Asia) Company Limited to recall Emtac 150 Tab 150mg (HK-59353) and Ranitid 150 Tab 150mg (HK-59429) respectively.

The above recalls were reported in the Drug News Issue No. 119, 120 and 121. 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.

Canada: Recall: APO-Metformin 500mg Tablet (Extended-Release)

On 4 February 2020, Health Canada announced that Apotex Inc. is recalling 8 lots of APO-Metformin 500mg Tablet (Extended-Release) (lot number: NV3242, NV3244, NV3245, NV3243, NV3247, NV3248, PX5334, PX5335) from wholesalers, healthcare establishments and retailers due to presence of NDMA above the interim acceptable concentration limit in affected lots.

In Hong Kong, Apo-Metformin XR 500 Modified-Release Tablets 500mg (HK-65083) is a pharmaceutical product registered by Hind Wing Co Ltd, and is a prescription-only medicine. As confirmed with Hind Wing Co Ltd, the affected lots have not been imported into Hong Kong.

As on 5 March 2020 in Hong Kong, there are 125 registered pharmaceutical products containing metformin. All products are prescription-only medicines.

Related news on the detection of NDMA in metformin products was previously issued by the Singapore Health Sciences Authority and other overseas drug regulatory authorities, and was reported in the Drug News Issue No. 122. The DH issued a letter to inform local healthcare professionals to draw their attention on 6 December 2019. The DH has contacted the certificate holders of all registered metformin products for follow up on the local impact of the issue, and collected samples of metformin-containing products in the local market for analysis. When there are any health risks identified and 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).

As on 5 March 2020, the DH has received 17 cases of ADR related to metformin. None of them is concluded to be related to the presence of NDMA. The DH will remain vigilant on the development of the issue and any safety update of the drug issued by overseas drug regulatory authorities for consideration of any action deemed necessary.

Patients who are taking metformin-containing products should not stop taking the medicines, but should seek advice from their healthcare professionals for proper arrangement.

UK: Lemtrada▼ (alemtuzumab): updated restrictions and strengthened monitoring requirements following review of serious cardiovascular and immune-mediated reactions

On 12 February 2020, the MHRA announced that a

review of the benefits and risks of alemtuzumab (including fatal reactions) in the treatment of multiple sclerosis has concluded and recommended a revised indication, additional contraindications, and strengthened monitoring requirements before, during and after treatment.

In May 2019, the MHRA informed of interim restrictions on the use of alemtuzumab (Lemtrada▼) for relapsing multiple sclerosis during an urgent European safety review of serious cardiovascular reactions occurring within a few days of infusion and of immune-mediated events.

The review concluded that serious cardiovascular reactions can rarely occur within 1 to 3 days of alemtuzumab infusions in people without any identifiable risk factors. Reactions included myocardial ischaemia, cerebral haemorrhage, arterial dissection of the cervicocephalic arteries, pulmonary alveolar haemorrhage, and non-immune thrombocytopenia. The review also found unpredictable and potentially fatal immune-mediated reactions can occur within months and up to at least 4 years after treatment with alemtuzumab. Reactions included autoimmune hepatitis, haemophagocytic lymphohistiocytosis, and acquired haemophilia A. The review also identified serious cases of Epstein-Barr virus reactivation reported after treatment, including hepatitis. Some patients developed more than one autoimmune disorder following treatment.

Alemtuzumab should now only be used in adults with highly active relapsing-remitting multiple sclerosis if they have not responded to a full and adequate course of treatment with another disease-modifying treatment or if they have rapidly evolving severe relapsing-remitting multiple sclerosis. New contraindications and risk minimisation measures have also been introduced and a letter sent to prescribers and dispensers of alemtuzumab in the UK.

The frequency of thrombocytopenia (including both immune and acute non-immune cases) associated with alemtuzumab is common (affecting up to 1 in 10 patients). The frequency of myocardial infarction, pulmonary alveolar haemorrhage, and arterial dissection is not known because these reactions were only observed in the post-marketing setting. However, estimated post-marketing reporting indicates that the rate of events occurring within a week of treatment were 2 cases per 10,000 patients for myocardial infarction; 3.6 per 10,000 patients for stroke; 1.6 per 10,000 patients for arterial dissection; and 4.3 per 10,000 patients for pulmonary alveolar haemorrhage. The frequency of acquired haemophilia A is uncommon (up to 1 in 100 patients) and the frequency of haemophagocytic lymphohistiocytosis is rare (up to 1 in 1000 patients). The frequency of autoimmune hepatitis is not known as this reaction was only observed in the post-marketing settings. The estimated post-marketing reporting rate was 10.7 cases of autoimmune hepatitis per 10,000 patients.

Healthcare professionals are advised:

Restricted indication

- Alemtuzumab should only be used as single disease-modifying therapy in adults with either:
  - highly active relapsing-remitting multiple sclerosis despite a full and adequate course of treatment with at least one disease-modifying therapy or
  - rapidly evolving severe relapsing-remitting multiple sclerosis defined as 2 or more disabling relapses in 1 year, and with one or more gadolinium enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2-lesion load compared to a recent MRI scan.

New contraindications and revised monitoring requirements

- Alemtuzumab is contraindicated in patients with: severe active infection until complete resolution, uncontrolled hypertension, a history of arterial dissection of the cervicocephalic arteries, a history of stroke, a history of angina or myocardial infarction, clotting abnormalities including treatment with antiplatelet or anticoagulant therapy, autoimmune diseases (apart from multiple sclerosis).
- Only administer alemtuzumab in a hospital with ready access to intensive care facilities.
- Monitor patients closely before, during, and after alemtuzumab infusions for cardiovascular reactions and non-immune thrombocytopenia.
- Monitor patients for autoimmune disorders for at least 48 months after the last infusion – some autoimmune reactions have been reported after this routine monitoring period.

Advice to give to patients

- Alert patients receiving alemtuzumab to the

signs and symptoms of serious adverse reactions described within a few days of an infusion and to seek urgent medical attention if they develop the following:

- chest pain, coughing up blood, or breathing difficulty;
- drooping of the face, severe headache, neck pain, weakness on one side, or difficulty speaking;
- skin or eyes turning yellow, or dark urine, abdomen pain, bleeding or bruising easily (signs of liver damage);
- fever, swollen glands, bruising, or rash.

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 March 2020, the DH has received 3 cases of ADR related to alemtuzumab, but these cases are not related to autoimmune hepatitis, haemophagocytic lymphohistiocytosis, acquired haemophilia A 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, 120 and 121. 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 of the Pharmacy and Poisons Board (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: Restrictions in use of cyproterone due to meningioma risk

On 14 February 2020, the EMA's Pharmacovigilance Risk Assessment Committee of the European Union (EU) has recommended that medicines with daily doses of 10 mg or more of cyproterone should only be used for androgen-dependent conditions such as hirsutism (excessive hair growth), alopecia (hair loss), acne and seborrhoea (excessively oily skin) once other treatment options, including treatment with lower doses, have failed. Once higher doses have started working, the dose should be gradually reduced to the lowest effective dose.

The medicines should only be used for reduction of sex drive in sexual deviations in men when other treatment options are not suitable.

There is no change in use of the medicines in men for prostate cancer.

The recommendations follow a review of the risk of the rare tumour meningioma with cyproterone. Overall, this side effect is rare: it may affect between 1 and 10 in 10,000 people, depending on the dose and duration of treatment. The risk increases with increasing cumulative doses (the total amount of medicine a patient has taken over time).

Available data do not indicate a risk for low-dose cyproterone medicines containing 1 or 2 milligrams cyproterone in combination with ethinylestradiol or estradiol valerate and used for acne, hirsutism, contraception, or hormone replacement therapy. However, as a precaution, they should not be used in people who have or have had a meningioma. This restriction is already in place for the higher dose medicines.

Doctors should monitor patients for symptoms of meningioma, which can include changes in vision, hearing loss or ringing in the ears, loss of smell, headaches, memory loss, seizures or weakness in arms and legs. If a patient is diagnosed with meningioma, treatment with cyproterone medicines must be stopped permanently.

As part of the ongoing surveillance of the safety of the medicines, companies marketing medicines containing 10 mg or more of cyproterone will be required to carry out a study to assess doctors' awareness of the risk of meningioma and how to avoid it.

Meningioma is a rare tumour of the membranes covering the brain and spinal cord. It is usually non-malignant and is not considered to be a cancer, but due to their location in and around the brain and spinal cord, meningiomas can cause serious problems.

Information for patients

- There is a risk of meningioma (a non-cancerous brain tumour) from medicines

containing cyproterone. The risk, which is very low, occurs especially when the medicines are taken at high doses (25 mg daily or more).
- For some uses – excess hair growth, hair loss, acne and oily skin – medicines containing 10 mg or more cyproterone should only be given when other treatment options, including lower-dose cyproterone medicines, have not worked or cannot be used. Once they have started working, the dose should be gradually reduced to the lowest dose that works.
- Cyproterone medicines should only be used to reduce sex drive in sexual deviations in men when other options for treatment are not suitable.
- Although there is no evidence of a risk for low-dose products containing cyproterone in combination with ethinylestradiol or estradiol valerate, as a precaution, these medicines should not be used in people who have or have had a meningioma. Higher-dose cyproterone-containing medicines already have this restriction not to use with meningioma.
- There is no change in the use of cyproterone medicines for prostate cancer.
- If they are taking a cyproterone medicine and have any questions about their treatment, talk to their doctor or pharmacist.

Information for healthcare professionals
- The occurrence of meningiomas (single and multiple) has been reported in association with the use of cyproterone acetate, primarily at doses of 25 mg/day and above.
- The risk increases with increasing cumulative doses of cyproterone acetate. Most cases have been reported after prolonged exposure (several years) to high doses of cyproterone (25 mg a day and above).
- Medicines containing 10 mg or more of cyproterone should only be used for hirsutism, androgenic alopecia, acne and seborrhoea once other treatment options, which could include low-dose cyproterone-containing medicines such as cyproterone acetate 2 mg/ ethinylestradiol 35 micrograms, have not worked. After clinical improvement, the dose should be gradually reduced to the lowest effective dose.
- Cyproterone medicines should only be used in men for reduction of sex drive in sexual deviations when other treatments are not appropriate.
- Healthcare professionals should monitor patients for clinical signs and symptoms of meningioma in line with clinical practice. Symptoms may be unspecific and include changes in vision, hearing loss or ringing in the ears, loss of smell, headaches that worsen with time, memory loss, seizures or weakness in extremities.
- If a patient treated with cyproterone acetate is diagnosed with meningioma, treatment with all cyproterone-containing products must be permanently stopped.
- Cyproterone acetate (1 and 2 mg) in combination with ethinylestradiol or estradiol valerate will be contraindicated in patients with a meningioma or history of meningioma. Higher-dose cyproterone medicines already have this contraindication.
- There is no change in the use of cyproterone medicines for prostate cancer. These medicines are used as antiandrogen treatment in inoperable prostate cancer, including for prevention of the initial flare-up in treatment with luteinizing hormone-releasing hormone agonists.
- The association of cyproterone acetate with meningioma was first added to the product information for medicines with cyproterone daily doses of 10 mg or more in 2009, with a contraindication for people with a history of meningioma.
- This review included recent results from a French epidemiological study showing a cumulative dose-dependent association between cyproterone acetate and meningioma (Weill et al) and an analysis by the French medicines agency ANSM (Agence nationale de sécurité du médicament et des produits de santé) of cases of meningioma with cyproterone use in France. Recent published literature and analysis of the EU database of adverse events, EudraVigilance, were also included.

In Hong Kong, there are three registered pharmaceutical products containing more than 10mg of cyproterone, namely, Androcur Tab 50mg (HK-46443), Procur Tab 50mg (HK-58614) and Apo-Cyproterone Tab 50mg (HK-55387); there are six registered pharmaceutical products containing 2mg cyproterone acetate in combination with ethinyloestradiol. All products are prescription-only medicines. As on 5 March 2020, the DH has not received any case of ADR related to cyproterone.

In light of the EMA's announcement, the DH issued a letter to inform local healthcare professionals to draw their attention on 17 February 2020, and the matter will be discussed by the Registration Committee.

Canada: Direct-acting antivirals - Assessing the potential risk of abnormal blood sugar levels (dysglycemia)

On 17 February 2020, Health Canada announced that it reviewed the potential risk of abnormal blood sugar (glucose) levels with the use of direct-acting antivirals (DAAs), including both high blood sugar levels (hyperglycemia) and low blood sugar levels (hypoglycemia). This assessment was triggered by updates made to the European product safety information for DAAs to include warnings about the use of these products in diabetic patients. These updates included recommendations to closely monitor glucose levels and modify patients' diabetic medications to prevent hypoglycemia.

DAAs are prescription drugs authorized for sale in Canada to treat chronic hepatitis C virus (HCV) infection. HCV infection can potentially decrease the liver's ability to perform its different roles, one of which is the control of blood sugar. A potential complication seen in patients with HCV infection is the loss of blood sugar control and higher levels of sugar in the blood, which can in turn lead to type II diabetes mellitus (T2DM). Patients with chronic HCV infection are 3.8 times more likely to have T2DM than non-infected individuals.

This review included the following products available in Canada: Daklinza (daclatasvir), Sovaldi (sofosbuvir), Harvoni (sofosbuvir, ledipasvir), Epclusa (sofosbuvir, velpatasvir), Vosevi (sofosbuvir, velpatasvir, voxilaprevir), Zepatier (grazoprevir, elbasvir) and Maviret (glecaprevir, pibrentasvir). These products may either contain a single DAA or multiple DAAs together.

At the time of the review, the Canadian Product Information for Daklinza (daclatasvir) already included the risk of dysglycemia in diabetic patients. Additionally, the Canadian Product Safety Information of sofosbuvir-containing products recommended the close monitoring of blood glucose levels in diabetic patients and suggested that the dose of diabetes medications may need to be adjusted during treatment.

Until 20 February 2019, Health Canada had received 564 Canadian cases reporting either hypoglycemia, hyperglycemia and/or new onset diabetes with the use of DAAs. Of these reports, 538 reports were excluded mainly for lack of information or because they were duplicates. Twenty-six (26) cases were retained. Health Canada also reviewed the scientific literature and found 10 additional international cases. Among a total of 36 case reports assessed,

- 24 case reports were related to hyperglycemia/ new onset diabetes, 8 were related to hypoglycemia/improvement in diabetes, and 4 were reported as other [1 case reported blood sugars as abnormal, 2 cases reported loss of blood sugar control and 1 case reported both increased (hyperglycemia) and decreased (hypoglycemia) blood sugar levels]. One (1) case of hyperglycemia also reported death.
- 2 case reports were assessed twice because one case reported the use of 2 DAAs initiated at different times. The events of hyperglycemia and death were both assessed for a cause-and-effect relationship (causality).
- 27 (including the reported death) were found to be possibly linked with the use of a DAA, 3 cases were unlikely to be linked to DAA use, and 8 cases could not be assessed due to insufficient information.

A search in VigiBase, the World Health Organization's Adverse Drug Reaction Database, found 735 cases related to dysglycemia reported in patients treated with DAAs. Given that chronic HCV can itself be linked with glucose disorders and that the VigiBase case reports contained limited information, the data could not be used to confirm or rule out a link between the use of DAAs and dysglycemia-related events.

This safety review also looked at information from 26 published studies in the scientific literature. There were a small number of reports of hypoglycemic events in the studies reviewed; no events related to hyperglycemia were reported. Diabetic patients were more vulnerable to the adverse reaction of hypoglycemia. In conclusion, the literature reviewed supports the finding that DAA treatment is associated with the improvement of glucose metabolism. Monitoring of blood sugar levels during treatment is advised.

A decrease in the dosage or the use of diabetes medications may be required in order to prevent the occurrence of symptoms or signs of hypoglycemia. The review of the literature identified biological

mechanisms to explain how DAAs could lead to hypoglycemia in diabetic patients. There was no clear process explaining how DAAs could promote the development of hyperglycemia or new-onset diabetes.

Health Canada's review has concluded that there is a link between the use of DAAs and the risk of dysglycemia. There have been reported cases of hyperglycemia/new onset diabetes in patients being treated with DAAs. However, there is stronger evidence that supports the development of hypoglycemia in diabetic patients treated with DAAs who experience high insulin sensitivity and a decreased need of diabetes medications.

Health Canada is working with the manufacturers to update the Canadian product safety information on DAAs to inform about the risk of dysglycemia in diabetic patients. Health Canada will continue to monitor safety information involving DAAs and dysglycemia and take appropriate and timely action if and when any new health risks are identified.

In Hong Kong, there are 8 registered pharmaceutical products which are direct-acting antivirals, namely, Sovaldi Tablets 400mg (containing sofosbuvir; HK-63501), Harvoni Tablets (containing sofosbuvir and ledipasvir; HK-63886), Epclusa Tablets 400mg/100mg (containing sofosbuvir and velpatasvir; HK-65046) and Vosevi Tablets (containing sofosbuvir, velpatasvir and voxilaprevir; HK-65775) which are registered by Gilead Sciences Hong Kong Limited; Maviret Tablets (containing glecaprevir and pibrentasvir; HK- 65653) which is registered by Abbvie Limited; Daklinza Tablets 60mg (containing daclatasvir; HK-64505) and Sunvepra Capsules 100mg (containing asunaprevir; HK-64506) which are registered by Bristol-Myers Squibb Pharma (HK) Ltd; and Zepatier Tablets (containing grazoprevir and elbasvir; HK-65571) which is registered by Merck Sharp & Dohme (Asia) Ltd. All products are prescription-only medicines. As on 5 March 2020, the DH has not received any case of ADR related to dysglycemia of the above-mentioned direct-acting antivirals.

Related news on risk of hypoglycemia of direct-acting antivirals was previously issued by the MHRA, and was reported in the Drug News Issue No. 110. The DH issued a letter to inform local healthcare professionals to draw their attention on 19 December 2018. In view of the above Health Canada's announcement, the DH issued a letter to inform local healthcare professionals to draw their attention on 18 February 2020, and the matter will be discussed by the Registration Committee.

Australia: Update: fluoroquinolone antibiotics and adverse events

On 27 February 2020, the Therapeutic Goods Administration (TGA) of Australia announced that, following the Medicines Safety Update article regarding fluoroquinolone antibiotics and risk of aortic aneurysm/dissection in April 2019, the Product Information (PI) for fluoroquinolone antibiotics have been updated to include more information about various potential adverse events. Fluoroquinolone antibiotics marketed in Australia include ciprofloxacin, norfloxacin and moxifloxacin.

The TGA investigated a safety signal relating to the rare but serious potential adverse event of aortic aneurysm and dissection associated with these medicines. An aortic aneurysm is an abnormal dilation of the main artery in the body that can in some circumstances rupture or dissect. This can lead to haemorrhage and in severe cases result in death.

Recent epidemiologic studies have shown an association between fluoroquinolone antibiotic use and aortic aneurysm and dissection. All PIs for fluoroquinolone antibiotics are being updated to include a precaution regarding this risk, particularly in the older population, which aligns with similar warnings being required by other international regulators (including the EMA and the United States (US) Food and Drug Administration (FDA)). The precaution advises that fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection.

During the TGA's investigation, it was also identified that the PIs for these medicines should be updated to ensure that precautions regarding the potential adverse events of dysglycaemia and psychiatric adverse reactions are included for all products and the information presented consistently. The precaution for dysglycaemia also contains reference to hypoglycaemia and

hypoglycaemic coma. The precaution for psychiatric adverse reactions is included under a separate heading titled 'Central Nervous System Effects'. It advises that these medicines have been associated with an increased risk of psychiatric adverse reactions including: toxic psychosis, psychotic reactions progressing to suicidal ideations/thoughts, hallucinations or paranoia; depression, or self-injurious behaviour such as attempted or completed suicide; anxiety, agitation, or nervousness; confusion, delirium, disorientation, or disturbances in attention; insomnia or nightmares; memory impairment. These reactions may occur following the first dose and if patients experience any of these symptoms, they should inform their doctor immediately and discontinue the drug.

In Hong Kong, there are 166 registered pharmaceutical products containing fluoroquinolones which are oral preparations or injectables for use in human, including ciprofloxacin (73 products), levofloxacin (56 products), moxifloxacin (6 products), norfloxacin (5 products), ofloxacin (25 products) and prulifloxacin (1 product). All products are prescription-only medicines. As on 5 March 2020, the DH has received 7 cases of ADR related to levofloxacin and 1 case related to moxifloxacin. One of the levofloxacin cases is related to insomnia. All other cases are not related to aortic aneurysm and dissection, dysglycaemia or psychiatric adverse reactions.

Related news on the risk of aortic aneurysm and dissection of fluoroquinolones was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 109, 110 and 116. The DH issued a letter to inform local healthcare professionals to draw their attention on 15 November 2018.

Related news on the risk of central nervous system effects (such as hallucinations and confusion) of fluoroquinolones was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 79, 81, 87, 88, 108 and 109. The DH issued letters to inform local healthcare professionals to draw their attention on 13 May 2016 and 8 October 2018.

Related news on the risk of serious low blood sugar levels and mental health side effects (such as disturbances in attention and delirium) of fluoroquinolones was previously issued by the US FDA, and was reported in the Drug News Issue No. 105. The DH issued a letter to inform local healthcare professionals to draw their attention on 11 July 2018.

In June 2019, the Registration Committee decided that the sales pack labels and/or package inserts of registered pharmaceutical products containing fluoroquinolones for systemic use should be updated and include safety information on the risk of aortic aneurysm and dissection and central nervous system effects, and to remain vigilant on any related safety updates issued by overseas drug regulatory authorities for serious low blood sugar levels and mental health side effects.

The DH will remain vigilant on safety update of the drugs issued by other overseas drug regulatory authorities.

Australia: Ferric carboxymaltose and low blood phosphorous

On 27 February 2020, the TGA announced that it is reminding health professionals that symptomatic hypophosphataemia is a known risk associated with use of ferric carboxymaltose and it is recommended that health professionals routinely evaluate patient risk factors before commencing this medicine and follow up at-risk patients. Ferric carboxymaltose is marketed in Australia under the brand name Ferinject.

Ferric carboxymaltose is known to cause mild asymptomatic transient hypophosphataemia. Ferric carboxymaltose is also associated with a rare risk of severe, symptomatic hypophosphataemia. In clinical trials, the minimum serum phosphate values were obtained after approximately 2 weeks, and in most cases returned to baseline values by 12 weeks following ferric carboxymaltose treatment. The Ferinject Product Information was updated in 2019 to include additional details about this precaution.

Mild hypophosphataemia is usually asymptomatic, but may present with pain, nausea, and asthenia. Severe hypophosphataemia may be associated with symptomatic physiological dysfunction. Acute manifestations include: muscular symptoms (weakness, asthenia, leading to progressive myopathy including cardiorespiratory compromise and death), neurological symptoms (tingling, altered mental status, seizures, paralysis), haematological changes.

Safety Update

The development of clinically significant hypophosphataemia following parenteral iron is more likely in patients on long-term iron replacement, and in those with lower baseline ferritin, gastrointestinal disorders, malnutrition or other causes of phosphate deficiency (low whole body phosphate).

Hypophosphataemia can be the cause of asthenia, fatigue, muscular weakness, breathlessness, tachycardia and headaches, which might otherwise be misdiagnosed as failure to respond to treatment of iron deficiency anaemia, therefore consider hypophosphataemia as a potential reason for a patients' symptoms continuing after use of ferric carboxymaltose.

In pregnancy the maximum cumulative dose is restricted to 1000 mg for patients with haemoglobin (Hb) ≥90 g/L, or 1500 mg in patients with Hb <90 g/L. No more than 1000 mg iron should be administered in one week.

The TGA adverse event database has 15 reports of hypophosphataemia with ferric carboxymaltose (including 14 where it was the sole suspected medicine). There were six reports of hypophosphataemia relating to iron polymaltose, and no reports involving other parenteral iron products. For ferric carboxymaltose, serum phosphate was reported in six cases, with severe hypophosphataemia (<0.3mmol/L) reported in four cases. Five cases reported systemic symptoms of hypophosphataemia (fatigue, malaise, lethargy) and skeletal manifestations of hypophosphataemia were reported in three cases. Most patients recovered with oral phosphate, calcitriol or with IV phosphate supplementation, but the outcome was reported as 'not recovered' in two cases. Time to onset, where reported, was generally from a few days up to two weeks after starting ferric carboxymaltose.

In Hong Kong, Ferinject Solution for Injection/ Infusion 100mg/2ml (HK-64137) and Ferinject Solution for Injection/Infusion 500mg/10ml (HK-64138) are pharmaceutical products registered by Zuellig Pharma Ltd, and are prescription-only medicines. As on 5 March 2020, the DH has not received any case of ADR related to ferric carboxymaltose. In light of the above TGA's announcement, the DH issued a letter to inform local healthcare professionals to draw their attention on 28 February 2020, and the matter will be discussed by the Registration Committee.

Drug Recall

DH endorsed recall of Synalar Ointment 0.025% (HK-06809)

On 14 February 2020, the DH endorsed a licensed wholesale dealer, DKSH Hong Kong Ltd (DKSH), to recall the product Synalar Ointment 0.025% (HK-06809) from the market due to a potential quality issue.

The DH received notification from DKSH that, during the stability testing of the above-mentioned product, the content of active ingredient was found slightly less than the specifications before the expiry of its 36-month shelf-life. The quality issue might affect the efficacy of the product. As a precautionary measure, DKSH is recalling the product from the market.

The above product is a prescription-only medicine which contains fluocinolone acetonide. It is a topical corticosteroid preparation used in the treatment of various skin disorders. According to DKSH, the product has been supplied to the Hospital Authority, local private hospitals, private doctors and pharmacies.

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

As on 5 March 2020, the DH has not received any adverse reaction report in connection with the product. Press release was posted on the Drug Office website on 14 February 2020 to alert the public of the product recall.

DH endorsed recall of Belviq Tablets 10mg

On 17 February 2020, the DH endorsed two licensed drug wholesalers, namely Pharmareg Consulting Co. Ltd. and Vantone Medical Supplies Co Ltd, to recall Belviq Tablets 10mg (Belviq) from the market due to a possible increased risk of cancer caused by the drug. Belviq is an unregistered pharmaceutical product imported for the treatment of particular patients.

The DH noted an announcement from the US FDA on 13 February 2020 that the manufacturer of Belviq was requested by the US FDA to voluntarily withdraw the product from the US market because

Drug Recall

the product was found to be associated with an increased occurrence of cancer. In light of this, the wholesalers are voluntarily recalling the products from the local market.

Belviq containing lorcaserin, is a prescription medicine used for the treatment of obesity. According to the wholesalers, the product has been supplied to one private hospital and to private doctors, solely for the treatment of particular patients.

People who have used the above product should stop using the product and consult their healthcare professionals.

As on 5 March 2020, the DH has not received any adverse reports in connection with the product concerned. A notice was posted on the Drug Office website on 17 February 2020 to alert the public of the product recall.

Drug Incident

Man arrested for suspected illegal sale of nicotine-containing liquids for electronic cigarettes

On 10 February 2020, the DH and the Police conducted a joint operation against the illegal sale of nicotine-containing liquids intended for use with electronic nicotine delivery systems, commonly known as electronic cigarettes.

Acting upon a public complaint, the DH found that a type of nicotine-containing liquid "RELX" was offered for sale in a retail store in Wan Chai. During the operation against the retail store in Wan Chai and its branch in Mong Kok on 10 February 2020, a number of other brands of nicotine-containing liquids, for use in electronic cigarette labelled with nicotine content were also found.

A 38-year-old man was arrested by the Police for suspected illegal sale and possession of Part 1 poisons and unregistered pharmaceutical products. In addition, a 21-year-old man and a 19-year-old woman were also arrested by the Police for suspected possession of Part 1 poisons and unregistered pharmaceutical products.

According to the Pharmacy and Poisons Ordinance (Cap. 138), nicotine-containing electronic cigarette products are classified as pharmaceutical products requiring registration with the Pharmacy and Poisons Board of Hong Kong before they can be sold in Hong Kong.

Smokers are advised to quit smoking for their own health and that of others. They are encouraged to make use of smoking cessation services through the DH's Integrated Smoking Cessation Hotline (1833 183). Information on smoking cessation can also be obtained from the DH's Tobacco and Alcohol Control Office website (www.taco.gov.hk).

Press release was posted on the Drug Office website on 11 February 2020 to alert the public of the drug incident.

News in Brief

Emergency Preparedness and Response for COVID-19 –Focusing On Business Continuity Arrangement

World Health Organization declared COVID-19 as a pandemic. The Centre for Health Protection of the Department of Health has promulgated a powerpoint titled "Emergency Preparedness and Response for COVID-19 – Focusing on Business Continuity Arrangement" (https://www.chp.gov.hk/files/pdf/formulating_business_continuity_plan.pdf).

As part of risk management, Healthcare sectors and Pharmaceutical Traders are advised to take note of the above and develop their own business continuity plan with a view to, among others, minimize the impact of potential supply disruptions of medical products.

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.