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

UK: Nivolumab (Opdivo): reports of cytomegalovirus (CMV) gastrointestinal infection or reactivation

On 18 October 2019, the Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom (UK) advised patients on nivolumab who present with diarrhoea or other symptoms of colitis, and those who do not respond to steroid treatment for immune-related colitis, should be investigated to exclude other causes, including infections such as CMV.

A European review of spontaneous and clinical trial reports received up to 31 August 2018, identified 20 serious cases worldwide suggestive of CMV infection or reactivation with nivolumab monotherapy. A further 8 cases were reported of either CMV infection or CMV hepatitis associated with nivolumab and ipilimumab combination therapy. Of the total 28 serious cases with nivolumab and nivolumab plus ipilimumab, 18 were suspected to be gastrointestinal CMV infection (10 cases for nivolumab and 8 cases for nivolumab plus ipilimumab).

Diarrhoea or colitis occurring after initiation of nivolumab must be promptly evaluated to exclude infectious or other alternate causes. For severe or life-threatening (grade 3 and 4) diarrhoea and immune-related colitis, nivolumab should be permanently discontinued and systemic high-dose intravenous corticosteroid therapy initiated.

In patients with immune-related colitis who are refractory to corticosteroids, the addition of an immunosuppressive agent should only be considered if other causes have been excluded, including CMV infection or reactivation.

Healthcare professionals are advised:

- Colitis is known to occur commonly in patients treated with nivolumab; advise patients to contact their healthcare professional immediately at the onset of symptoms of colitis (including diarrhoea, blood in stools, or abdominal pain).
- If patients on nivolumab present with diarrhoea or colitis, investigate possible causes, including infections; perform a stool infection work-up and screen for CMV.
- For patients with immune-related colitis that is corticosteroid refractory, use of an additional immunosuppressive agent should only be considered if other causes are excluded using appropriate laboratory tests and additional examinations (including screening for CMV using viral polymerase chain reaction biopsy, and for other viral, bacterial, and parasitic causes).
- Report suspected adverse drug reactions (ADRs) associated with nivolumab.

In Hong Kong, Opdivo Concentrate for Solution for Infusion 40mg/4ml (HK-64231) and Opdivo Concentrate for Solution for Infusion 100mg/10ml (HK-64232) are pharmaceutical products registered by Bristol-Myers Squibb Pharma (HK) Ltd., and are prescription-only medicines.

As on 5 November 2019, the Department of Health (DH) has received 50 cases of ADR for nivolumab but none of them were related to CMV infection. In light of the above MHRA's announcement, the DH issued a letter to inform local healthcare professionals to draw their attention on 21 October 2019.

EU: Lemtrada for multiple sclerosis: measures to minimise risk of serious side effects

On 31 October 2019, the European Medicines

Agency (EMA) of the European Union (EU) announced that the Pharmacovigilance Risk Assessment Committee (PRAC) has recommended restrictions on the use of Lemtrada (alemtuzumab) in patients with relapsing remitting multiple sclerosis (RRMS). The recommendations reflect the PRAC's review of reports concerning rare but serious effects, including deaths, from immune-mediated conditions (caused by the body's defence system not working properly) and serious heart, circulation and bleeding disorders, including stroke. Immune-mediated conditions can occur many months after treatment while serious disorders of the heart, circulation and bleeding may develop within days of receiving Lemtrada.

The PRAC has recommended restricting Lemtrada for use in adults with RRMS that is highly active despite adequate treatment with at least one disease-modifying therapy or if the disease is worsening rapidly with at least two disabling relapses in a year and brain-imaging showing new damage. Also, Lemtrada must no longer be used in patients with certain heart, circulation or bleeding disorders or in patients who have auto-immune disorders other than multiple sclerosis.

New measures have been recommended for identifying and promptly dealing with adverse effects that might occur after treatment with Lemtrada. It should be given in a hospital with ready access to intensive care facilities and specialists who can manage serious adverse reactions.

The PRAC has also recommended updating the physician's guide and the patient information pack with advice to minimise the risk of serious heart, circulation and bleeding disorders that may occur shortly after the infusion (drip) as well as autoimmune conditions that could occur many months after the last Lemtrada treatment.

The PRAC recommendations will be sent to the Committee for Medicinal Products for Human Use (CHMP), which will adopt the Agency's final opinion.

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 November 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 and 114. 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: Xeljanz to be used with caution for all patients at high risk of blood clots

On 31 October 2019, the EMA announced a review by the PRAC 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 PRAC is recommending that Xeljanz should be used with caution in 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 unless there is no suitable alternative treatment. Further, the PRAC is recommending that patients older than 65 years of age should be treated with Xeljanz only when there is no alternative treatment.

Patients at high risk of blood clots include those 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 who take combined hormonal contraceptives, are receiving hormone replacement therapy, are undergoing major surgery or are immobile. Doctors should also consider other factors that may increase the risk of blood clots including age, obesity, diabetes, hypertension or smoking.

These recommendations follow the PRAC's review of an ongoing study (study A3921133) in patients with rheumatoid arthritis and an increased risk of

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cardiovascular disease. This study showed an increased risk of blood clots in deep veins and in the lungs with both the 5 mg and 10 mg twice daily doses of Xeljanz as compared with patients taking tumor necrosis factor (TNF) inhibitors. The PRAC also re-assessed additional data from earlier studies. All data combined showed that the risk of blood clots was higher in patients taking Xeljanz, especially with 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 product information for Xeljanz will be updated with new warnings and recommendations based on data from the study and will list blood clots as an uncommon side effect occurring in between 1 in 1,000 and 1 in 100 patients. The PRAC has also recommended updating the physician's guide and the patient alert card with advice to minimise the risk of blood clots. Patients who have questions about their treatment or their risk of blood clots should contact their doctor.

The PRAC recommendations will be sent to the CHMP, which will adopt the Agency's final opinion.

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 November 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 and 117. The DH issued a letter to inform local healthcare professionals to draw their attention on 29 July 2019. As previously reported, the matter will be discussed by the Registration Committee.

Drug Recall

DH endorsed recall of Mitomycin-C powder for injection products

On 10 October 2019, the DH endorsed five licensed drug wholesalers, namely Tai Tong Co Ltd (Tai Tong); Four Seasons International Limited (Four Seasons); Trackcircle.com Limited (Trackcircle); Sino-Asia Pharmaceutical Supplies Ltd (Sino-Asia); and Vantone Medical Supplies Co Ltd (Vantone) to recall all Mitomycin-C powder for injection products from the market due to a potential quality issue.

The recall covers registered Mitomycin-C powder for injections as well as unregistered products imported by the companies for the treatment of particular patients. The affected products are listed below:

Wholesaler	Product(s)
Tai Tong	Mitomycin-C powder for injection 10mg KYOWA (HK-10969) Mitomycin-C powder for injection 2mg and 10mg KYOWA
Four Seasons	Mitomycin-C powder for injection 2mg and 10mg KYOWA
Trackcircle	Mitomycin-C powder for injection 10mg KYOWA
Sino-Asia	Mitomycin-C powder for injection 2mg KYOWA
Vantone	Mitomycin-C powder for injection 2mg KYOWA

The DH received notification that the production of the active drug substance, i.e. mitomycin, of the above products did not fully comply with the Good Manufacturing Practice requirements and that the sterility of the substance could not be guaranteed. Although the products passed relevant tests and met the specifications, the companies are voluntarily recalling the products from the market as a precautionary measure.

The products, which contain mitomycin, are prescription medicines used mainly for the treatment of bladder cancer. According to the companies, the products were supplied to the local healthcare sector including the Hospital Authority, private hospitals and local doctors, while some have been exported to Macao.

People who have used the above products are advised that they should consult their healthcare professionals if in doubt or feeling unwell.

As on 5 November 2019, the DH has not received any case of ADR in connection with the products concerned. Press release was posted on the Drug Office website on 10 October 2019 to alert the public of the products recall.

Drug Recall

DH endorsed recall of Epadoren Solution for Injection 50mg/2ml (HK-61752)

On 11 October 2019, the DH endorsed a licensed drug wholesaler, Hind Wing Co Ltd (Hind Wing), to recall a ranitidine-containing product, namely Epadoren Solution for Injection 50mg/2ml (HK-61752), from the market as a precautionary measure due to the potential presence of an impurity in the product.

The DH received notification from Hind Wing on 11 October 2019 that the manufacturer of the product suspected that the above product may contain an impurity, *N*-nitrosodimethylamine (NDMA), based on recent overseas announcements on the said impurity. NDMA is classified as a probable human carcinogen based on results from laboratory tests. As a precautionary measure, Hind Wing is voluntarily recalling the affected product from the market.

The above product is a prescription medicine used for the treatment of gastric diseases. According to Hind Wing, the product has been supplied to private hospitals, local doctors, veterinary surgeons and pharmacies.

As on 5 November 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 11 October 2019 to alert the public of the product recall.

Overall situation related to detection of NDMA in ranitidine

As on 5 November 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 November 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 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 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 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).

The above recalls endorsed by the DH from 24

September 2019 to 30 September 2019 were reported in the Drug News Issue No. 119. 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.

DH endorsed recall of one batch of Human Albumin Octapharma 20% Infusion (HK-59932)

On 11 October 2019, the DH endorsed a licensed medicine wholesaler Trenton-Boma Ltd (Trenton-Boma) to voluntarily recall one batch (batch number: L828A6682) of Human Albumin Octapharma 20% Infusion (HK-59932) from the market due to a potential quality issue.

The DH received notification from Trenton-Boma on 11 October 2019 that the manufacturer of the product indicated that the production of the above batch has deviated from the processes approved by the European authority. Although the manufacturer considered that the quality of the product was not compromised, the company is recalling the affected batch as a precautionary measure.

The product, which contains human albumin, is a prescription medicine for plasma volume replacement. According to Trenton-Boma, the affected batch has been supplied to the Hospital Authority, private doctors and veterinary surgeons. People who have used the above product should consult healthcare professionals if in doubt.

As on 5 November 2019, the DH has not received any case of ADR related to the product. Press release was posted on the Drug Office website on 11 October 2019 to alert the public of the product recall.

DH endorsed recall of three batches of Nutriflex Omega Special Emulsion for Infusion (HK-60999)

On 31 October 2019, the DH endorsed a licensed medicine wholesaler, B. Braun Medical (HK) Ltd, to recall three batches of Nutriflex Omega Special Emulsion for Infusion (HK-60999) from the market due to a potential quality issue.

The affected products are listed below:

Pack size	Batches
1,250 ml	174738051, 182838052
1,875ml	174938051

The DH received notification from B. Braun that products of the above-mentioned batches might have deviations in pH value, colouration and quality of emulsion, probably due to possible damage of the overwrapping of the product bags. As a precautionary measure, B. Braun has recalled the affected batches of the product.

The above product, mainly containing fatty acids, amino acids, electrolytes and glucose, is a parenteral nutrition preparation for nutrient supplement when oral or enteral nutrition is not feasible. According to B. Braun, the affected batches have been supplied to the Hospital Authority and private hospitals.

Patients who require use of the above product should seek advice from their healthcare professionals for appropriate arrangements. There are alternative medicines available on the market with similar indications.

As on 5 November 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 31 October 2019 to alert the public of the product recall.

A product containing any western drug ingredient must be registered under the Pharmacy and Poisons Ordinance before it can be sold in Hong Kong. Part 1 poisons should be sold at registered pharmacies under the supervision of registered pharmacists. Illegal sale or possession of Part 1 poisons and unregistered pharmaceutical products are offences under the Pharmacy and Poisons Ordinance (Cap. 138). The maximum penalty is a fine of $100,000 and two years' imprisonment for each offence. Antibiotics can only be supplied at registered pharmacies by registered pharmacists or under their supervision and upon a doctor's prescription. They should only be used under the advice of a doctor. Illegal sale or possession of antibiotics are offences under the Antibiotics Ordinance (Cap. 137) and the maximum penalty is a $30,000 fine and one year's imprisonment for each offence.

Under the Import and Export Ordinance (Cap. 60), pharmaceutical products must be imported or exported under and in 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.

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

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Adverse Drug Reaction (ADR) Reporting:

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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.