Drug News
藥 物 情 報

Issue Number 139

This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in May 2021 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

European Union: PRAC concludes review of signal of facial swelling with COVID-19 vaccine Comirnaty

On 7 May 2021, the European Medicines Agency (EMA) announced that its Pharmacovigilance Risk Assessment Committee (PRAC) has recommended a change to Comirnaty's product information. After reviewing all the available evidence, including cases reported to the European database for suspected side effects (EudraVigilance) and data from the scientific literature, PRAC considered that there is at least a reasonable possibility of a causal association between the vaccine and the reported cases of facial swelling in people with a history of injections with dermal fillers (soft, gel-like substances injected under the skin). Therefore, PRAC concluded that facial swelling in people with a history of injections with dermal fillers should be included as a side effect in section 4.8 of the summary of product characteristics (SmPC) and in section 4 of the patient information leaflet (PIL) for Comirnaty. The benefit-risk balance of the vaccine remains unchanged.

In Hong Kong, the above product is not a registered pharmaceutical product under the Pharmacy and Poisons Ordinance (Cap. 138). The COVID-19 vaccine by Fosun Pharma/BioNTech (i.e. Comirnaty) is authorised for emergency use in Hong Kong in accordance with the Prevention and Control of Disease (Use of Vaccines) Regulation (Cap. 599K). Related news was previously issued by EMA, and was reported in the Drug News Issue No. 137. The Department of Health (DH) will remain vigilant on safety update of the product issued by other overseas drug regulatory authorities.

European Union: PRAC continues to closely review Comirnaty and COVID-19 Vaccine Moderna for unusual blood clots with low blood platelets

On 7 May 2021, the EMA announced that PRAC is closely monitoring whether mRNA vaccines might also be linked to cases of rare, unusual blood clots with low blood platelets, a side effect that has been reported in Vaxzevria and COVID-19 vaccine Janssen. Following a review of reports of suspected side effects, the PRAC considers at this stage that there is no safety signal for the mRNA vaccines. Only few cases of blood clots with low blood platelets have been reported. When seen in the context of the exposure of people to the mRNA vaccines, these numbers are extremely low, and their frequency is lower than the one occurring in people who have not been vaccinated. In addition, these cases do not seem to present the specific clinical pattern observed with Vaxzevria and COVID-19 Vaccine Janssen. Overall, the current evidence does not suggest a causal relation. EMA will continue to monitor this issue closely and communicate further if necessary.

In Hong Kong, the above products are not registered pharmaceutical products under the Pharmacy and Poisons Ordinance (Cap. 138). The COVID-19 vaccine by Fosun Pharma/BioNTech (i.e. Comirnaty) is authorised for emergency use in Hong Kong in accordance with the Prevention and Control of Disease (Use of Vaccines) Regulation (Cap. 599K). The DH will remain vigilant on safety update of the product issued by other overseas drug regulatory authorities.

European Union: More flexible storage conditions for BioNTech/Pfizer's COVID-19 vaccine

On 17 May 2021, EMA announced that its human medicines committee (Committee for Medicinal

Products for Human Use, CHMP) has recommended a change to the approved storage conditions of Comirnaty, the COVID-19 vaccine developed by BioNTech and Pfizer, that will facilitate the handling of the vaccine in vaccination centres across the European Union (EU).

This change extends the approved storage period of the unopened thawed vial at 2-8°C (i.e. in a normal fridge after taking out of deep-freeze conditions) from five days to one month (31 days). The change was approved following assessment of additional stability study data submitted to EMA by the marketing authorisation holder. Increased flexibility in the storage and handling of the vaccine is expected to have a significant impact on planning and logistics of vaccine roll-out in EU Member States.

The changes described will be included in the publicly available information on Comirnaty and will be implemented by the marketing authorisation holder in updated product labelling. Users are reminded to always refer to the label and package leaflet of the supplied product for the correct storage information.

In Hong Kong, the above product is not a registered pharmaceutical product under the Pharmacy and Poisons Ordinance (Cap. 138). The COVID-19 vaccine by Fosun Pharma/BioNTech (i.e. Comirnaty) is authorised for emergency use in Hong Kong in accordance with the Prevention and Control of Disease (Use of Vaccines) Regulation (Cap. 599K). Related news was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 136, 137, and 138. The DH will remain vigilant on safety update of the product issued by other overseas drug regulatory authorities.

Canada: Summary Safety Review: Opdivo (nivolumab): Assessing the potential risks of certain blood disorders, and cytokine release and tumor lysis syndromes

On 19 May 2021, Health Canada announced that it reviewed the potential risks of autoimmune hemolytic anemia, aplastic anemia, cytokine release syndrome and tumor lysis syndrome with the use of Opdivo (nivolumab), either alone or in combination with Yervoy (ipilimumab). These reviews were triggered by safety information provided by the manufacturer and information from the published medical literature.

Autoimmune hemolytic anemia is a condition where the body's immune system attacks and destroys its own red blood cells. Aplastic anemia is a condition where the body stops producing enough new blood cells. Cytokine release syndrome is an inflammatory reaction throughout the body, characterized by fever and multiple organ damage. Tumor lysis syndrome is a rapid breakdown of cancer cells with the release of substances into the blood that cause blood chemical imbalance and organ damage.

Health Canada reviewed information received from the manufacturer, as well as information from searches of the Canada Vigilance database, international databases, and published literature. At the request of Health Canada, the manufacturer performed safety reviews of Opdivo, used alone or in combination with Yervoy, and the risks of autoimmune hemolytic anemia, aplastic anemia, cytokine release syndrome and tumor lysis syndrome. The manufacturer concluded that there is a possible link between Opdivo and autoimmune hemolytic anemia, and agreed to include this risk in the Canadian Product Monograph (CPM). Health Canada further reviewed the risks of aplastic anemia, cytokine release syndrome and tumor lysis syndrome with Opdivo, used alone or in combination with Yervoy:

- For aplastic anemia, Health Canada had received 3 Canadian cases, but only 1 case met the criteria for further assessment. Therefore, the safety review focused on 16 case reports (1 Canadian and 15 foreign). Of the 16 case reports, 7 (1 Canadian) reports were found to be probably linked to the use of Opdivo, 8 cases were possibly linked, and 1 case was considered unlikely to be linked with Opdivo use.
- For cytokine release syndrome, Health Canada had received 6 Canadian cases, but only 1 case met the criteria for further assessment. Therefore, the safety review focused on 13 reports (1 Canadian and 12 foreign). A potential link between cytokine release syndrome and the use of Opdivo could not be ruled out for these 13 reports because 7 reports (1 Canadian) were found to be probably linked and 6 reports were possibly linked.
- For tumor lysis syndrome, Health Canada had received 2 Canadian reports. The 2 reports did not meet the criteria for further assessment. Therefore, Health Canada's review focused on 12 foreign cases. A potential link between tumor lysis syndrome and the use of Opdivo

could not be ruled out for these 12 cases because 2 cases were considered probably linked, and 10 cases were considered possibly linked.

Health Canada's review of the available information concluded that there may be a link between Opdivo, used alone or in combination with Yervoy, and the risk of autoimmune hemolytic anemia, aplastic anemia, cytokine release syndrome and tumor lysis syndrome. The Canadian product safety information for Opdivo has been updated to include the risk of autoimmune hemolytic anemia in the Warning and Precautions section of the CPM. Health Canada is working with the manufacturer of Opdivo to also include the risks of aplastic anemia, cytokine release syndrome and tumor lysis syndrome in the CPM.

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 7 June 2021, the DH has received 87 cases of adverse drug reaction related to nivolumab, of which 2 cases are related to tumor lysis syndrome, and one case is related to both cytokine release syndrome and tumor lysis syndrome. In light of the above Health Canada's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 20 May 2021 and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

The United Kingdom: Levothyroxine: new prescribing advice for patients who experience symptoms on switching between different levothyroxine products

On 19 May 2021, Medicines and Healthcare products Regulatory Agency (MHRA) announced new prescribing advice for patients who experience symptoms on switching between different levothyroxine products.

Levothyroxine is authorised for the control of hypothyroidism. In the United Kingdom, prescribing of levothyroxine is usually generic, with no named product specified on the prescription. Patients may thus be changed between different levothyroxine products according to what is available at their local pharmacies, with the prescriber generally unaware of the specific product that the patient is taking at any particular time. This generic prescribing approach is supported by strict United Kingdom regulatory requirements for licensing to ensure compatibility (bioequivalence) between products. Nevertheless, the MHRA receives reports of patients experiencing adverse events on switching between different levothyroxine products. The MHRA has conducted a review of the available data and sought advice from the Commission on Human Medicines (CHM) as to whether any regulatory action is needed to minimise the risk of adverse events on switching between different levothyroxine products.

For the 5-year period between 1 January 2015 and 31 December 2019, the MHRA received 335 Yellow Cards reporting one or more of the terms 'product substitution issue', 'condition aggravated' or 'drug ineffective' with levothyroxine. The majority of reports were received from patients rather than healthcare professionals, with 47 of the cases having a healthcare professional reporter. Associated symptoms were mostly consistent with hypothyroidism or hyperthyroidism, and included fatigue, headache, malaise, anxiety, palpitations, pruritus, nausea, myalgia, dizziness, arthralgia, feeling abnormal, alopecia, depression, abnormal weight gain, and insomnia. Of the 335 cases, 12 reported a recurrence of their symptoms after a second trial with the medicine concerned. Only 27 of the 335 cases included reference to thyroid function test results. Of these, 9 suggested a hypothyroid state, with 4 hyperthyroid and 14 euthyroid. In most cases, thyroid function test data from before the product switch were not available to confirm that thyroid function was well controlled before the switch, or to indicate whether a substantial change in parameters within reference range had occurred.

The underlying causes for the symptoms experienced by patients switching between levothyroxine products are generally unclear. Potential causative factors could include:

- gastrointestinal comorbidities potentially affecting levothyroxine absorption
- concomitant use of medication reducing gastric acidity, which can also affect levothyroxine absorption
- very low thyroid reserve
- intolerance or allergy to an excipient in a particular brand
- specific genotypes relating to thyroid hormone synthesis or thyroid receptor function

For the most part, the symptoms experienced on

switching levothyroxine tablet formulations could indicate the need for dose adjustment. However, some patients experience symptoms despite thyroid function testing showing them as biochemically euthyroid.

These symptoms experienced by a minority of patients are acknowledged in United Kingdom professional guidelines. These guidelines note that although generic prescribing of levothyroxine is appropriate for the vast majority of patients, in rare cases a patient may require a specific levothyroxine brand to be prescribed. In some patients, better control of thyroid function may be achieved with oral solution forms of levothyroxine than with tablets.

CHM considered the reports in the United Kingdom and advised that levothyroxine should continue to be prescribed generically for most patients. If a patient reports symptoms after their brand of levothyroxine is changed, healthcare professionals are advised to consider testing of thyroid function and follow the 'Advice for healthcare professionals' section below.

Advice for healthcare professionals:

- generic prescribing of levothyroxine remains appropriate for the majority of patients and the licensing of these generic products is supported by bioequivalence testing
- a small proportion of patients treated with levothyroxine report symptoms, often consistent with thyroid dysfunction, when their levothyroxine tablets are changed to a different product; these cases are noted in United Kingdom professional guidelines
- if a patient reports symptoms after changing their levothyroxine product, consider testing thyroid function
- if a patient is persistently symptomatic after switching levothyroxine products, whether they are biochemically euthyroid or have evidence of abnormal thyroid function, consider consistently prescribing a specific levothyroxine product known to be well tolerated by the patient
- if symptoms or poor control of thyroid function persist despite adhering to a specific product, consider prescribing levothyroxine in an oral solution formulation

In Hong Kong, there are 9 registered pharmaceutical products containing levothyroxine. All products are prescription-only medicines. As on 7 June 2021, the DH has received 3 cases of adverse drug reaction related to levothyroxine, but these cases are not related to product switching. The risk of adverse effects (e.g. manifestations of hypothyroidism or hyperthyroidism) on switching between different levothyroxine products is documented in overseas reputable drug references such as the "Martindale: The Complete Drug Reference" and "AHFS Drug Information". The DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

European Union: EMA reminds physicians to use Tecentriq with nab-paclitaxel for treating breast cancer: Update

On 21 May 2021, EMA announced that its review of the IMpassion131 study has confirmed that the results do not show that combining Tecentriq (atezolizumab) with conventional paclitaxel slows down the progression of the cancer or reduces deaths in patients with locally advanced or metastatic triple-negative breast cancer that cannot be surgically removed. Therefore, in line with the current product information, Tecentriq should continue to be used only in combination with nab-paclitaxel.

In Hong Kong, Tecentriq Concentrate For Solution For Infusion 1200mg/20ml (HK-65567), Tecentriq Concentrate For Solution For Infusion 1200mg/20ml (HK-66341) and Tecentriq Concentrate For Solution For Infusion 840mg/14ml (HK-66613) are registered pharmaceutical products containing atezolizumab. All products are registered by Roche Hong Kong Limited, and are prescription-only medicines. As on 7 June 2021, the DH has received 91 cases of adverse drug reaction related to atezolizumab.

Related news was previously issued by the United States Food and was reported in the Drug News Issue No. 131. Letters to inform local healthcare professionals were issued by the DH on 5 October 2020. In Hong Kong, Tecentriq is currently approved in combination with nab-paclitaxel for the treatment of breast cancer. The DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

Safety Update

Canada: Summary Safety Review: Pomalyst (pomalidomide) and Thalomid (thalidomide): Assessing the potential risk of progressive multifocal leukoencephalopathy

On 27 May 2021, Health Canada announced that it reviewed the potential risk of a rare brain infection known as progressive multifocal leukoencephalopathy (PML) with the use of Pomalyst or Thalomid following reported cases of PML in patients taking Pomalyst. PML is an opportunistic infection in the brain caused by the John Cunningham (JC) virus. It is most frequently associated with a weakened immune system. PML is often fatal; therefore, it is important to detect it early so it can be appropriately managed.

Health Canada reviewed the available information from searches of the Canada Vigilance database, the World Health Organization's Adverse Drug Reaction Database, published literature and information provided by the manufacturer. At the time of the review, Health Canada had not received any Canadian reports of PML related to Pomalyst or Thalomid use. The safety review assessed 25 international case reports of PML in patients treated with pomalidomide (16 cases) or thalidomide (9 cases). For pomalidomide, 15 cases showed a possible link between this medication and PML, and 1 case did not have enough information to be further assessed. For thalidomide, 6 cases showed a possible link, while 3 cases were unlikely to be linked. All cases had other contributing factors, such as other medications taken by the patients that could have been possible causes of PML, or medical conditions that could have affected the patients' immune system and/or infection risk. Multiple myeloma itself is a risk factor for PML. Health Canada's review of the scientific literature did not find a clear mechanism to explain how Pomalyst or Thalomid could lead to PML.

Health Canada's review of the available information concluded that there is a possible link between Pomalyst or Thalomid and the risk of PML. The Canadian product safety information for Pomalyst has been updated to include a warning for the risk of PML. Health Canada is working with the manufacturer to update the Thalomid Canadian product information to include this rare safety issue.

In Hong Kong, there are 4 registered pharmaceutical products containing pomalidomide, namely Pomalyst Capsules 2mg (HK-64089), Pomalyst Capsules 3mg (HK-64090), Pomalyst Capsules 1mg (HK-64091) and Pomalyst Capsules 4mg (HK-64092). All products are registered by Celgene Limited, and are prescription-only medicines. There is no registered pharmaceutical product containing thalidomide. As on 7 June 2021, the DH has received 3 cases of adverse drug reaction related to pomalidomide, but these cases are not related to PML. In light of the above Health Canada's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 28 May 2021 and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Drug Recall

Recall of pms-Irbesartan Tablet 150mg and pms-Irbesartan Tablet 300mg

On 31 May 2021, the DH endorsed a licensed drug wholesaler, Trenton-boma Ltd (T-Boma), to recall two batches of the following products from the market as a precautionary measure due to the presence of an impurity in the product.

Name of Product	Hong Kong Registration Number	Batch Number
pms-Irbesartan Tablet 150mg	HK-61098	617492
pms-Irbesartan Tablet 300mg	HK-61097	624193

The DH received notification from T-Boma today that the overseas manufacturer of the product is initiating a voluntary recall of certain batches of products due to the presence of a higher than accepted level of azido impurity in the affected batches. According to T-Boma, the two affected batches of tablets have been imported and supplied in Hong Kong. As a precautionary measure, T-Boma is voluntarily recalling those batches from the market.

Azido impurity is considered a mutagen that can cause a change in the DNA of a cell and may increase the risk of cancer, but the risk for the azido impurity to cause cancer in humans is unknown. Overseas drug regulatory authorities have been reviewing the safety impact of azido impurity

Drug Recall

found in medicinal products. The DH will closely monitor the development of the issue and any safety updates regarding the drug issued by overseas drug regulatory authorities for consideration of any action deemed necessary.

The above products are prescription medicines used to lower blood pressure. According to T-Boma, the affected batches have been supplied to private doctors and hospital, as well as pharmacies.

As on 7 June 2021, the DH has not received any adverse reaction reports in connection with the product. Press release was posted the Drug Office website on 31 May 2021 to alert the public of the product recall.

Drug Incident

Public urged not to buy or consume unlabelled slimming products with controlled ingredients

On 6 May 2021, the DH appealed to the public not to buy or consume unlabelled slimming products that may contain controlled medicine ingredients and might be dangerous to health.

Acting upon intelligence, it was found that someone was offering for sale via a social media platform an unlabelled slimming product and claiming the product to be "Fat burning pills". Samples of the product were obtained for analysis and the Government Laboratory's results confirmed that the samples contained sibutramine, a Part 1 poison under the Pharmacy and Poisons Ordinance (Cap. 138). The DH's investigation is continuing.

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

Press release was posted on the Drug Office website on 6 May 2021 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 $50,000 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: Adverse Drug Reaction and Adverse Event Following Immunization Unit,
Drug Office, Department of Health,
Room 1856, 18/F, Wu Chung House,
213 Queen's Road East,
Wanchai, Hong Kong

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.