# Drug News
# 藥 物 情 報

**Issue Number 129**

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

**Canada: Brilinta (ticagrelor): Assessing the potential risks of a worsening of a slow and irregular heartbeat (bradyarrhythmia) and partial or complete block in the transmission of heart impulses (second- and third-degree atrioventricular block)**

On 6 July 2020, Health Canada announced that it reviewed the potential risk of a worsening of a slow and irregular heartbeat (bradyarrhythmia) in patients with a history of bradyarrhythmia as well as the risk of developing a partial or complete block in the transmission of heart impulses (second- and third-degree atrioventricular [AV] block) in patients treated with Brilinta. The safety review was triggered by published international reports of second- and third-degree AV block in patients taking Brilinta.

Bradyarrhythmia is a slow and irregular heart rate of less than 60 beats per minute. In second- and third-degree AV block, the transmission of heart impulses (electrical signals) from the upper chambers of the heart (atria) to the lower chambers (ventricles) is partly or completely interrupted, leading to bradyarrhythmia.

Health Canada reviewed the available information from searches of the Canada Vigilance database, international databases, and published literature. The review of the risk of worsening of bradyarrhythmia focused on 18 international cases of patients with a history of bradyarrhythmia who were taking Brilinta. At the time of the review, no Canadian cases of worsening of bradyarrhythmia related to the use of Brilinta in patients with a history of bradyarrhythmia have been reported to Health Canada. Of the 18 case reports, 15 reports were found to be possibly linked to the use of Brilinta, one report was not likely to be linked, and 2 reports did not have enough information to be assessed. Assessing whether the worsening of bradyarrhythmia was related to use of Brilinta in these reports was challenging due to several contributing factors including other existing medical conditions (present in all 18 case reports) and patients taking other medications besides Brilinta (present in more than half of the case reports). Of the 18 case reports, one resulted in death; however, a link between the death and use of Brilinta was not established due to lack of information.

Health Canada also assessed the risk of second- or third-degree AV block related to the use of Brilinta. At the time of the review, 2 Canadian cases of second- and third-degree AV block in patients who used Brilinta have been reported to Health Canada. The review focused on 44 case reports (2 Canadian and 42 international) of patients with or without a history of bradyarrhythmia, who suffered from second- or third-degree AV block while taking Brilinta. Of the 44 case reports, 2 reports were found to be probably linked to the use of Brilinta, 40 cases (including 2 Canadian cases) were possibly linked, one report was not likely to be linked, and one did not have enough information to be assessed. Assessing whether AV blocks were related to use of Brilinta in these reports was challenging due to several contributing factors including other existing medical conditions (present in all 44 case reports) and patients taking other medications in addition to Brilinta (present in more than half of the case reports). Of the 44 case reports, 9 resulted in death. Of the 9 reports, 3 reports were found to be possibly linked with use of Brilinta, one report was not likely to be linked, and 5 reports did not have enough information to be assessed. In the 3 reports where the death outcome was deemed possibly linked to the use of Brilinta, assessing whether the death was related to the use of Brilinta was challenging since other medical conditions, such as coronary artery

disease, could have been the cause of death.

Health Canada also assessed 4 population-based studies found in the scientific literature in order to determine the link between the use of Brilinta and the risk of worsening of the bradyarrhythmia and second- or third-degree AV block. Health Canada's review of these studies did not give additional information beyond what was obtained from the above case reports.

Health Canada's review concluded that there may be a link between the use of Brilinta and the risk bradyarrhythmia, including second- and third-degree AV block. Health Canada will work with the manufacturer to update the product safety information for Brilinta, and to inform healthcare professionals and patients about these risks.

In Hong Kong, there are 2 registered pharmaceutical products containing ticagrelor, namely Brilinta Tab 90mg (HK-61187) and Brilinta Tablets 60mg (HK-64706). Both products are registered by AstraZeneca Hong Kong Ltd, and are prescription-only medicines. As on 5 August 2020, the Department of Health (DH) has received 6 cases of adverse drug reaction (ADR) related to ticagrelor, but these cases are not related to bradyarrhythmia or atrioventricular block. In light of the above Health Canada's announcement, the DH issued a letter to inform local healthcare professionals to draw their attention on 7 July 2020, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board (Registration Committee).

**Canada: Status of ranitidine drugs in Canada**

On 23 July 2020, Health Canada announced an update on the status of ranitidine drugs in Canada, including enhanced safety measures Health Canada is putting in place to detect an impurity called *N*-nitrosodimethylamine (NDMA).

In September 2019, Health Canada directed companies to stop distributing ranitidine drugs in Canada as an interim, precautionary measure while it assessed the risk of NDMA detected in some drugs. Since then, companies have recalled products from the Canadian market because they contained or potentially contained NDMA above acceptable levels.

Health Canada has been evaluating the issue to identify potential causes and risk mitigation measures. Based on its evaluation, Health Canada permitted companies wishing to resume sales to do so provided they test every batch of ranitidine product before releasing it and regularly throughout its shelf life, to demonstrate that products do not contain higher than accepted levels of NDMA. Some companies resumed sales in January and February 2020.

While the root cause of NDMA in ranitidine remains unclear, Health Canada has since assessed additional information, including some evidence that suggests that levels of NDMA in ranitidine products may increase over time and when stored at higher than room temperature. In addition, some limited data suggest that NDMA may form in the body after ranitidine has been consumed, but this has not been confirmed.

As a result of its assessment of this additional information, Health Canada is now directing companies wishing to sell ranitidine products in Canada to undertake the following safety measures:

- continue to test every batch of ranitidine product before releasing it and test it regularly throughout its shelf life;
- conduct more frequent testing if NDMA is detected within a certain range below the accepted limit, to enable faster detection of any increases in NDMA;
- conduct additional testing to evaluate the potential for NDMA formation under different storage conditions (e.g., above room temperature); and
- provide all of the above test data to Health Canada, along with any information to help further evaluate the potential formation of NDMA from ranitidine in the body.

These strengthened measures will enable Health Canada to more actively monitor for NDMA in ranitidine products over their shelf life, and to take action as needed. They will also facilitate the collection of data to increase the understanding of NDMA formation.

As on 5 August 2020, there are 61 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 August 2020, 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, and was reported in the Drug News Issue No. 122, 123, 124 and 126. The DH issued letters to inform local healthcare professionals to draw their attention on 18 September 2019 and 2 April 2020. 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.

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. On 16 June 2020, the Registration Committee discussed the matter and decided to keep vigilant on any safety update issued by overseas drug regulatory authorities for consideration of any action deemed necessary. Patients who are taking ranitidine-containing products should seek advice from their healthcare professionals for proper arrangement, e.g. use of alternative medicines with similar uses.

**US: Opioid pain relievers or medicines to treat opioid use disorder: FDA recommends healthcare professionals discuss naloxone with all patients when prescribing**

On 23 July 2020, the United States (US) Food and Drug Administration (FDA) announced that it is requiring drug manufacturers for all opioid pain relievers and medicines to treat opioid use disorder (OUD) to add new recommendations about naloxone to the prescribing information. This will help ensure that healthcare professionals discuss the availability of naloxone and assess each patient's need for a naloxone prescription when

opioid pain relievers or medicines to treat OUD are being prescribed or renewed.

Opioid pain relievers are medicines that can help manage pain when other treatments and medicines are not able to provide enough pain relief. Certain opioids are also used to treat OUD. Opioids have serious risks, including misuse and abuse, addiction, overdose, and death. Naloxone can help reverse opioid overdose to prevent death.

The misuse and abuse of illicit and prescription opioids and the risks of addiction, overdose, and death are a public health crisis in the US. As a result, the FDA is committed to encouraging healthcare professionals to raise awareness of the availability of naloxone when they are prescribing and dispensing opioid pain relievers or medicines to treat OUD. The FDA held discussions about naloxone availability with the Anesthetic and Analgesic Drug Products and the Drug Safety and Risk Management Advisory Committees, which recommended that all patients being prescribed opioids for use in the outpatient setting would benefit from a conversation with their healthcare professional about the availability of naloxone.

**Healthcare professionals are recommended to:**

- Discuss the availability of naloxone with all patients when prescribing or renewing an opioid analgesic or medicine to treat OUD.
- Consider prescribing naloxone to patients prescribed medicines to treat OUD and patients prescribed opioid analgesics who are at increased risk of opioid overdose.
- Consider prescribing naloxone when a patient has household members, including children, or other close contacts at risk for accidental ingestion or opioid overdose.
- Additionally, even if the patients are not receiving a prescription for an opioid analgesic or medicine to treat OUD, consider prescribing naloxone to them if they are at increased risk of opioid overdose.
- Educate patients and caregivers on how to recognize respiratory depression and how to administer naloxone. Inform them about their options for obtaining naloxone as permitted by their individual state dispensing and prescribing requirements or guidelines for naloxone. Emphasize the importance of calling 911 or getting emergency medical help right away, even if naloxone is administered.

In Hong Kong, there are registered pharmaceutical products which are opioid pain relievers or medicines used to treat opioid use disorder. There are also registered pharmaceutical products containing naloxone. As on 5 August 2020, the DH has received cases of ADR related to opioid pain relievers (such as pethidine and tramadol), or medicines used to treat opioid use disorder (such as methadone). The DH has not received any case of ADR related to naloxone. In light of the above FDA's announcement, the DH issued a letter to inform local healthcare professionals to draw their attention on 24 July 2020. Healthcare professionals are advised to balance the risk of possible adverse effects against the benefit of treatment. The DH will remain vigilant on safety update of the drugs issued by other overseas drug regulatory authorities.

**Canada: Non-prescription pain relief products containing codeine are not recommended for use in people under 18 years of age**

On 31 July 2020, Health Canada announced that it is advising Canadians that people under 18 years of age should not use non-prescription pain relief products containing codeine. Non-prescription codeine-containing pain relief products were previously not recommended for children and youth under 12 years of age.

This recent action is an extension of Health Canada's previous advice to Canadians that people under 18 years of age should not use cough and cold products that contain opioids, including codeine. Health Canada continues to encourage patients, parents and caregivers to consult with their healthcare professional about the use of prescription pain relief products containing codeine or other opioids.

These actions are a result of Health Canada reviewing all available information on non-prescription codeine-containing pain relief products, which demonstrated that using opioids at a young age may contribute to the development of problematic substance use later in life.

Health Canada is working with manufacturers of non-prescription pain relief products containing codeine to update their product safety information to reflect Health Canada's recommendation that people under 18 years of age should not use these products.

**Information for patients, parents and caregivers:**

- Ask their healthcare professional about alternatives to non-prescription codeine-containing products to treat pain in people under 18 years of age.
- All health products, including non-prescription pain relief products, should be used with caution and stored out of the reach of children to prevent accidental ingestion.
- Always read the labels on their medications and any additional safety information provided by their pharmacist or other healthcare professional.
- There are alternatives to codeine-containing products available for people under 18 years of age to treat pain.

**Information for healthcare professionals:**

- Advise patients, parents and caregivers on the proper use of opioid-containing health products.

In Hong Kong, there are 357 registered pharmaceutical products containing codeine.

News related to the limitation of the use of opioid-containing cough and cold medicines to adults (18 years of age and older) was previously issued by the US FDA, China National Medical Products Administration and Health Canada, and was reported in the Drug News Issue No. 99 and 112. The DH issued a letter to inform local healthcare professionals to draw their attention on 12 January 2018. In June 2018, the Registration Committee discussed the matter and decided to remain vigilant on safety update issued by other overseas drug regulatory authorities.

As on 5 August 2020, the DH has received 4 cases of ADR related to codeine.

The DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities for consideration of any action deemed necessary.

**UK: Systemically administered VEGF pathway inhibitors: risk of aneurysm and artery dissection**

On 31 July 2020, the Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom (UK) announced the risk of aneurysm and artery dissection associated with the use of systemically administered vascular endothelial growth factor (VEGF) pathway inhibitors.

A recent European review concluded that all systemically administered VEGF pathway inhibitors may promote the formation of aneurysm and artery dissection. The product information for all systemically administered VEGF pathway inhibitors in the UK has been updated to include a warning about the risk of aneurysm and artery dissection and to recommend carefully considering these risks before initiating in patients with risk factors, such as hypertension. Patients who receive a systemic VEGF pathway inhibitor should be monitored and treated for hypertension in accordance with recommendations in the Summary of Product Characteristics for the relevant systemic VEGF pathway inhibitor. Action should also be considered for other modifiable risk factors such as smoking. The patient information leaflet for all products in the UK will also include advice for patients to inform their doctor or nurse if they have had a previous aneurysm or dissection.

Before the latest safety review, the product information of four systemic VEGF pathway inhibitors in the UK included aortic dissection (Kisplyx▼ and Lenvima▼), aneurysm rupture (Inlyta), or aortic aneurysm and dissection (Sutent) as side effects. In addition, the product information for all systemic VEGF pathway inhibitors already described the risk of hypertension, which is an important predisposing factor for artery dissection and aneurysm.

As part of the review, a search of the European database of worldwide reports of suspected ADRs identified 660 case reports of aneurysm or artery dissection for VEGF pathway inhibitors up to 31 December 2018. The most frequently reported adverse events were aortic dissection (n=163), aneurysm (n=146), retinal aneurysm (n=93), aortic aneurysm (n=89), ruptured aortic aneurysm (n=43), intracranial aneurysm (n=34) and aneurysm ruptured (n=31). Fatal cases have been reported, mainly in relation to aortic aneurysm rupture and aortic dissection. Of the 529 case reports where medical history was available, most (74%) reported risk factors, most commonly hypertension (49%). Other risk factors reported included diabetes mellitus, hypercholesterolaemia or hyperlipidaemia, a previous history of aortic aneurysm, cardiovascular disease and tobacco use. Aortic dissection and aortic aneurysm were more

frequently reported in older patients (aged 65 years or older).

Based on the available data it is difficult to estimate the magnitude of the risk of aneurysm and artery dissection with systemic VEGF pathway inhibitors, therefore the risk of these adverse reactions is included in the product information with a frequency category of not known. Clinical trial data suggest that the frequency of artery dissection and aneurysm in patients receiving systemic VEGF pathway inhibitors ranges from rare (0.02% of participants) to uncommon (0.15% of participants exposed). The data do not allow for differentiation in the risk of artery dissection and aneurysm between the different systemic VEGF pathway inhibitors and clinical trial data were not available for 6 products.

The mechanism by which systemically administered VEGF pathway inhibitors can cause aneurysm or artery dissection is unclear but may be due to impairment of vascular wall integrity as well through hypertension or aggravation of pre-existing hypertension. Aortic dissection is a rare but life-threatening event with an estimated annual incidence of between 2.9 to 3.5 cases per 100,000 people. It is usually accompanied by sudden, severe abdominal, chest, or back pain. Most abdominal aortic aneurysms are asymptomatic, and it is therefore difficult to establish their prevalence, however a national screening programme in the UK that enrols men at age years 65 years suggests a prevalence of about 1.3% in this population. The most common symptom of a ruptured aortic aneurysm is sudden and severe pain in the abdomen or back. Ruptured aortic aneurysms are associated with a high mortality rate.

The risk of artery dissection or aortic aneurysm is increased in the presence of risk factors such as hypertension, diabetes mellitus, family history of aneurysm, coronary, cerebrovascular or peripheral arterial disease, tobacco use and hyperlipidaemia. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease and the use of fluoroquinolones are also risk factors.

Systemically administered VEGF pathway inhibitors authorised in the UK include: Avastin, Zirabev▼ and Mvasi▼ (bevacizumab); Caprelsa▼ (vandetanib); Cabometyx▼ and Cometriq▼ (cabozantinib); Cyramza (ramucirumab); Fotivda▼ (tivozanib); Iclusig▼ (ponatinib); Inlyta (axitinib); Kisplyx▼ and Lenvima▼ (lenvatinib); Nexavar (sorafenib); Ofev and Vargatef (nintedanib); Stivarga (regorafenib); Sutent (sunitinib); Votrient (pazopanib); and Zaltrap (aflibercept).

The review concluded that there was insufficient evidence to determine that these risks apply to the two VEGF pathway inhibitors that are administered by intravitreal injection, ranibizumab (Lucentis) and aflibercept (Eylea).

**Healthcare professionals are advised:**

- Use of systemically administered VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms or artery dissections.
- Aneurysms or artery dissections are thought to occur infrequently in patients taking systemic VEGF pathway inhibitors, but some fatal cases have been reported, mainly in relation to aortic aneurysm rupture and aortic dissection.
- Before initiating a systemic VEGF pathway inhibitor, carefully consider the risk of aneurysm and artery dissection in patients with risk factors such as hypertension, history of aneurysm, smoking, diabetes mellitus, coronary, cerebrovascular or peripheral arterial disease, and hyperlipidaemia; other risk factors include Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, and the use of fluoroquinolones.
- In patients who receive a systemic VEGF pathway inhibitor, reduce as far as possible any modifiable risk factors such as smoking and hypertension.
- Monitor patients for and treat hypertension in accordance with recommendations in the Summary of Product Characteristics in the UK for the relevant systemic VEGF pathway inhibitor.

In Hong Kong, there are registered pharmaceutical products for systemic administration containing bevacizumab (6 products), vandetanib (2 products), cabozantinib (3 products), ramucirumab (2 products), ponatinib (2 products), axitinib (2 products), lenvatinib (2 products), sorafenib (3 products), nintedanib (4 products), regorafenib (1 product), sunitinib (4 products), pazopanib (4 products) and aflibercept (1 product). All products are prescription-only medicines. There is no registered pharmaceutical product containing tivozanib.

# Safety Update

Related news was previously issued by Health Canada and Singapore Health Sciences Authority, 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 4 December 2018. In September 2019, the Registration Committee discussed the matter and decided to remain vigilant on safety update issued by other overseas drug regulatory authorities.

As on 5 August 2020, the DH has received cases of ADR related to bevacizumab (62 cases), vandetanib (1 case), cabozantinib (19 cases), ramucirumab (14 cases), ponatinib (1 case), axitinib (26 cases), lenvatinib (6 cases), sorafenib (16 cases), nintedanib (3 cases), regorafenib (31 cases), sunitinib (9 cases), pazopanib (7 cases) and aflibercept (7 cases), but these cases are not related to aneurysm or artery dissection.

In light of the above MHRA's announcement, the matter will be further discussed by the Registration Committee.

# Drug Recall

**DH endorsed batch recall of Timo-Comod Eyedrops 0.5% (HK-44928)**

On 15 July 2020, the DH endorsed Reich Pharm Limited (Reich Pharm), the registration certificate holder of Timo-Comod Eyedrops 0.5% (Timo-Comod) (HK-44928), to recall one batch (Batch Number: 296015) of Timo-Comod from the market due to potentially defective bottle pumps. The product is distributed in Hong Kong by Rich Plan International Limited.

The DH received notification from Reich Pharm that the valve of the product's bottle pump of the above-mentioned batch might be defective, which may lead to unpredictable delivery of drop volume and in turn compromise the therapeutic effect. As a precautionary measure, Reich Pharm is recalling the affected batch of the product.

The above product, containing timolol, is a prescription eye drops product used for the treatment of glaucoma. According to Reich Pharm, the affected batch has been supplied to the Hospital Authority, private hospitals, private doctors and local pharmacies.

People who have used the above product should consult their healthcare professionals if in doubt or feeling unwell. As on 5 August 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 15 July 2020 to alert the public of the product recall.

**DH endorsed recall of two metformin-containing products**

On 22 July 2020, the DH endorsed two licensed drug wholesalers, Suntol Medical Ltd. (Suntol) and Hovid Limited (Hovid), to recall two metformin-containing products from the market as a precautionary measure due to the presence of an impurity in the products. The affected products are Glucofit Extended-Release Tablets 500mg (HK-64640) from Suntol and Diabetmin XR Extended-Release Tablets 500mg (HK-63333) from Hovid.

Based on overseas reports, the DH collected samples of all extended-release formulations of metformin products registered in Hong Kong for analysis. Test results from the Government Laboratory confirmed that samples of the above two products contained NDMA. As a precautionary measure, the wholesalers are voluntarily recalling the above two products.

NDMA is classified as a probable human carcinogen based on results from laboratory tests and overseas drug regulatory authorities have been reviewing the safety impact of NDMA found in some medicinal products including metformin.

The above products, containing metformin, are prescription medicines used for the treatment of diabetes mellitus. According to the wholesalers, the products have been supplied to local private doctors and pharmacies.

As on 5 August 2020, the DH has not received any adverse reaction reports in connection with the products. Press release was posted on the Drug Office website on 22 July 2020 to alert the public of the products recall.

**<u>Overall situation related to detection of NDMA in metformin</u>**

As on 5 August 2020 in Hong Kong, there are 122 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 various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 122 and 124. 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). The following is the main content of the press statement issued previously:

- On 11 March 2020, the DH endorsed a licensed wholesale dealer, the International Medical Company Ltd, to recall 3 batches of Metformin-Teva 500mg Tablets (HK-60334) (batch number: 16532717, 16532817 and 16532917) from the market due to the potential presence of NDMA in the product.

The above recall was reported in the Drug News Issue No. 125. As on 5 August 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.

**DH endorsed recall of Nexavar Tablet 200mg (HK-55409)**

On 23 July 2020, the DH endorsed a registration certificate holder, Bayer Healthcare Limited (Bayer), to recall all batches of Nexavar Tablet 200mg (HK-55409) from the market because the package insert of the product does not match with the registered one. The product is distributed in Hong Kong by Zuellig Pharma Ltd.

The DH received notification from Bayer on 23 July 2020 that the package insert of the product was different from that of the registered one. Although the differences were mainly textual in nature and did not involve indication or dosage, bearing with the unapproved package insert render the product unregistered. In this connection, Bayer voluntary recalls the product from the market.

The above product, containing sorafenib, is a prescription medicine used for the treatment of various cancers. According to Bayer, the product has been supplied to the Hospital Authority, private hospitals, private doctors and local pharmacies.

Patients who have used the above product should seek advice from their healthcare professionals if in doubt. A notice was posted on the Drug Office website on 23 July 2020 to alert the public of the product recall.

**DH endorsed recall of "ChloraPrep One-Step 3ml Applicator - Clear"**

On 24 July 2020, the DH endorsed a licensed wholesale dealer Becton Dickinson Asia Limited (BD) to recall all batches of "ChloraPrep One-Step 3ml Applicator - Clear" from the market due to potential growth of a fungus.

The DH received notification from BD on 24 July 2020 evening that the company is recalling the above-mentioned product because they have found that if the product is stored at 30 degree Celsius and 75 per cent relative humidity for more than six months, there may be growth of a fungus *Aspergillus penicillioides* due to a breach in the package integrity. The contaminated applicator may affect patient's safety during invasive procedure.

"ChloraPrep One-Step 3ml Applicator - Clear", containing chlorhexidine and isopropyl alcohol, is used for patient preoperative skin preparation. The product is not registered in Hong Kong. In order to tighten the control of chlorhexidine-containing products, with effect from 8 July 2020, skin antiseptics containing chlorhexidine are generally considered as pharmaceutical product requiring registration.

The product was distributed by United Italian Corporation (H.K.) Ltd. According to the distributor, the product had been supplied to the Hospital Authority, private hospitals and local

doctors before July 2020.

Members of the public who have used the product should consult their healthcare professional if in doubt. As on 5 August 2020, the DH has not received any adverse event against the product. Press release was posted on the Drug Office website on 24 July 2020 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*

**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.***