# Drug News
# 藥 物 情 報

**Issue Number 119**

***This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in September 2019 with relevant information update before publish. For the latest news and information, please refer to public announcements or the website of the Drug Office of the Department of Health (http://www.drugoffice.gov.hk).***


## Safety Update

### Singapore: Biotin interference with clinical laboratory tests

On 11 September 2019, the Health Sciences Authority (HSA) of Singapore announced that biotin can significantly interfere with certain clinical laboratory tests, resulting in incorrect laboratory values. Potential biotin interference has been identified with oral products containing ≥150mcg biotin per dose unit and parenteral products containing ≥60mcg biotin per dose unit. If undetected, the incorrect test results might lead to misdiagnosis or inappropriate patient management.

There are three parenteral products containing biotin registered in Singapore, namely Cernevit, Soluvit N and Tamipool. All three products are multivitamin infusions containing ≥60mcg biotin per dose unit. Biotin can also be found in health supplements for oral use, such as multivitamins, prenatal vitamins, and products promoting hair, skin and nail growth.

Some laboratory tests are based on a streptavidin-biotin interaction to determine a variety of biomarkers, including hormones, cardiac markers, tumour markers, and infection markers, as well as to determine the concentration of drugs. Biotin is not expected to interfere with laboratory tests when taken at levels found naturally in food or at amounts near the recommended daily intake of 30mcg. However, in patients taking biotin-containing products at higher doses, competition with biotinylated reagents may result in clinically significant false results (i.e. incorrectly increased or decreased) in these tests. This poses a potential risk for delayed diagnosis, wrong diagnoses and unnecessary treatments. The risk of obtaining incorrect test results due to biotin is higher in patients receiving high-dose biotin therapy for certain conditions (e.g. multiple sclerosis or rare metabolic disorders), renal failure patients, neonates, children and pregnant women. The popularity of dietary supplements marketed for improving hair, skin and nail health has also been reported to contribute towards the increasing use of high-dose biotin.

In January 2019, the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) concluded that there was sufficient evidence to support a potential interference with clinical laboratory tests of oral medicinal products containing ≥150mcg biotin per dose unit, and parenteral medicinal products containing ≥60mcg biotin per dose unit. The EMA PRAC requested for the product information of these products to be updated to reflect this risk.

Apart from the EMA PRAC, the United States (US) Food and Drug Administration (FDA) had issued a safety communication in November 2017 to alert the public, healthcare professionals, laboratory personnel and laboratory test developers on the potential interference of laboratory tests with the use of biotin. The FDA had highlighted an increase in the number of reported adverse events related to this risk, including one death arising from falsely low troponin test results. The agency informed that it would work with stakeholders to better understand the issue, and to develop additional future recommendations for safe testing in patients who had taken high levels of biotin when using laboratory tests that use biotin technology.

The HSA has not received any adverse event report

in Singapore of biotin interference resulting in incorrect laboratory results. The package inserts of parenteral biotin-containing products in Singapore are being updated to include warnings on this interference, and a company-initiated Dear Healthcare Professional Letter was also issued for Soluvit N in May 2019 to highlight this risk.

Healthcare professionals are advised to consider the possibility of biotin interference when ordering laboratory tests for their patients and when interpreting laboratory results (especially if the results do not match the clinical presentation and/or other investigations). This may involve asking their patients about the use of biotin health supplements, including those marketed for hair, skin and nail growth, as biotin in the patients' specimens could result in the generation of incorrect test results. As a general precaution, some hospital laboratories in Singapore have advised patients to stop biotin therapy for at least 12 hours before blood sample collection is done to minimise falsely increased/ decreased laboratory results arising from biotin interference.

In Hong Kong, there are 132 registered pharmaceutical products containing biotin. As on 8 October 2019, the Department of Health (DH) has not received any case of adverse drug reaction (ADR) related to biotin. Related news was previously issued by the FDA and the HSA, and was reported in the Drug News Issue No. 97. The DH issued a letter to inform local healthcare professionals to draw their attention on 29 November 2017. The DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

## Singapore: Risk of acute pancreatitis and congenital malformations associated with the use of carbimazole or thiamazole

On 11 September 2019, the HSA announced that it would like to bring the attention of healthcare professionals to overseas case reports of acute pancreatitis with the use of carbimazole or thiamazole (synonym: methimazole) and to update on the known risk of congenital malformations associated with these products.

Overseas cases of carbimazole- and thiamazole-induced acute pancreatitis have been reported in literature. The majority of these cases involved females and patients aged 55 years and above, who developed acute pancreatitis within two to three weeks following initiation of carbimazole or thiamazole therapy (range: four days to three months). Known risk factors for pancreatitis (e.g. hypertriglyceridemia, chronic alcohol consumption, cholelithiasis, autoimmune diseases) were ruled out by the reporting physician or denied by the patient. Positive dechallenge was seen in all these patients, whose symptoms and examination findings improved following withdrawal of carbimazole or thiamazole and conservative treatment. Reintroduction of carbimazole or thiamazole to some patients led to recurrent acute pancreatitis with a decreased time-to-onset (TTO) (i.e. after the single or second dose of carbimazole or thiamazole in most of the cases), suggesting an immune-mediated mechanism. Although the sulfhydryl group of carbimazole and thiamazole has been postulated to be involved in the drug-induced autoimmunisation, its exact role in the development of acute pancreatitis remains to be confirmed.

Carbimazole and thiamazole are known to cross the placenta and are suspected to cause congenital malformations. Recent studies have provided further evidence of an increased risk of congenital malformations with carbimazole or thiamazole use during pregnancy. A recent meta-analysis of 12 published case-control and cohort studies demonstrated that exposure to carbimazole or thiamazole during pregnancy increased the risk of congenital malformations compared to no antithyroid drug exposure (odds ratio [OR] 1.88; 95% confidence interval [CI] 1.33-2.65). In addition, a Korean nationwide cohort study using a prescription claims database observed a 1.3-fold (95% CI 1.06-1.63) increased congenital malformation risk with exposure to thiamazole during the first trimester compared with pregnancies without antithyroid drug prescriptions, corresponding to 17 additional congenital malformation cases (95% CI 1.94-32.15) per 1,000 live births. The authors also found that high cumulative thiamazole dose (> 495mg) was associated with a 1.87-fold (95% CI 1.06-3.30) increased congenital malformation risk compared with low cumulative dose (up to 126mg). The mechanism underlying carbimazole or thiamazole

embryopathy remains unknown, and the contribution of maternal hyperthyroidism to the risk of congenital malformations is poorly understood.

The HSA has received one report of pancreatitis associated with carbimazole use in a 69-year-old female in Singapore, with no further details provided. No reports of congenital malformations associated with carbimazole or thiamazole use have been received in Singapore. In March 2019, a Dear Healthcare Professional Letter was issued by the product registrant for Thyrozol to inform healthcare professionals about these safety concerns. The package inserts for all carbimazole- and thiamazole-containing products in Singapore will be updated to warn about these risks, including a new contraindication for use in patients with a history of acute pancreatitis after administration of carbimazole or thiamazole, and a new recommendation to use effective contraceptive measures during treatment.

Healthcare professionals are advised to take into consideration the above safety information when prescribing carbimazole and thiamazole. If acute pancreatitis is suspected, healthcare professionals are advised to consider immediate discontinuation of carbimazole and thiamazole. These drugs should also be avoided in patients with a history of acute pancreatitis following administration of carbimazole or thiamazole as re-exposure might result in recurrence of acute pancreatitis with a decreased TTO. Healthcare professionals are also encouraged to counsel women of childbearing potential on the importance of using effective and reliable contraception during treatment with carbimazole or thiamazole. When carbimazole or thiamazole is prescribed during pregnancy following a positive benefit versus risk assessment, the lowest effective dose should be used together with close maternal, foetal and neonatal monitoring.

In Hong Kong, there are 6 registered pharmaceutical products containing carbimazole, and 2 products containing methimazole (also known as thiamazole). All products are prescription-only medicines. As on 8 October 2019, the DH has received one case of ADR related to carbimazole, but this case is not related to acute pancreatitis or congenital malformations. The DH has not received any case of ADR related to methimazole.

Related news was previously issued by the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA) and the HSA, and was reported in the Drug News Issue No. 112. The DH issued a letter to inform local healthcare professionals to draw their attention on the risk of acute pancreatitis of the drugs on 19 February 2019. The matter has been discussed by the Registration Committee of the Pharmacy and Poisons Board (Registration Committee) on 17 September 2019 and decided that the sales pack labels and/or package inserts of registered pharmaceutical products containing carbimazole or methimazole should include safety information about acute pancreatitis and its use in fertility, pregnancy and lactation. It is also noted that congenital defects of carbimazole and methimazole have already been documented in overseas reputable drug references such as the "Martindale: The Complete Drug Reference". The DH will remain vigilant on safety update of the drugs issued by other overseas drug regulatory authorities.

## US: FDA warns about rare but severe lung inflammation with Ibrance, Kisqali, and Verzenio for breast cancer

On 13 September 2019, the US FDA warned that Ibrance (palbociclib), Kisqali (ribociclib), and Verzenio (abemaciclib) used to treat some patients with advanced breast cancers may cause rare but severe inflammation of the lungs. The FDA has approved new warnings about this risk to the prescribing information and patient package insert for the entire class of these cyclin-dependent kinase 4/6 (CDK 4/6) inhibitor medicines. The overall benefit of CDK 4/6 inhibitors is still greater than the risks when used as prescribed.

The FDA reviewed CDK 4/6 inhibitors cases from completed and ongoing clinical trials undertaken by manufacturers and their postmarket safety databases that described specific types of inflammation of the lungs, called interstitial lung disease (ILD) and pneumonitis. Across the entire drug class, there were reports of serious cases, including fatalities.

Patients should notify their healthcare professional right away if they have any new or worsening symptoms involving their lungs, as they may indicate a rare but life-threatening condition that can lead to death. Symptoms to watch for including difficulty or discomfort with breathing and shortness of breath while at rest or with low activity. They should not stop taking their medicine without first talking to their healthcare professionals.

Healthcare professionals should monitor patients regularly for pulmonary symptoms indicative of ILD and/or pneumonitis. Signs and symptoms may include hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic examinations in patients in whom infectious, neoplastic, and other causes have been excluded. Interrupt CDK 4/6 inhibitor treatment in patients who have new or worsening respiratory symptoms, and permanently discontinue treatment in patients with severe ILD and/or pneumonitis.

In Hong Kong, there are 3 registered pharmaceutical products containing palbociclib, and one product containing ribociclib. All products are prescription-only medicines. There is no registered pharmaceutical product containing abemaciclib. As on 8 October 2019, the DH has received ADR related to palbociclib (104 cases) and ribociclib (8 cases), but these cases are not related to interstitial lung disease or pneumonitis. In light of the above FDA's announcement, the DH issued a letter to inform local healthcare professionals to draw their attention on 16 September 2019, and the matter will be discussed by the Registration Committee.

## Canada: Health Canada advises Canadians to exercise caution when taking gabapentin or pregabalin with opioids

On 17 September 2019, Health Canada announced that it is advising Canadians about the increased risk of opioid overdose and serious side effects when taking gabapentin (e.g., Neurontin) or pregabalin (e.g., Lyrica) with an opioid.

Gabapentin is authorized in Canada to treat epilepsy and pregabalin is authorized in Canada to treat nerve pain. Both drugs belong to a class of drugs called gabapentinoids, which have been marketed in Canada since 1994.

Opioids are drugs that are used primarily to treat pain. They include both prescription and non-prescription medications such as codeine, fentanyl, morphine, oxycodone, hydromorphone, tramadol, tapentadol, hydrocodone, methadone and buprenorphine. Opioids may also be prescribed for other conditions, such as moderate to severe diarrhea, moderate to severe cough, and opioid use disorder. Increasingly, opioids such as fentanyl can also be found in illegal drugs, including heroin and cocaine. Consuming as little as a few grains of salt worth of fentanyl alone can be deadly.

When used with opioids, gabapentinoids increase the risk of opioid overdose. Serious side effects of using gabapentinoids and opioids at the same time include respiratory depression (slowed breathing), increased sedation (sleepiness), dizziness, fainting, and death. If people suspect an overdose, call for emergency help, administer naloxone if they have it, and stay with the person. Naloxone is a fast-acting drug that can temporarily reverse the effects of an opioid overdose.

Patients are advised:

- Consult their healthcare practitioner if they currently use or have used gabapentinoids or opioids and are concerned about their health.
- Know the signs of an opioid overdose.
- Stay informed and consult their healthcare practitioner on what other drugs and substances can increase the risk of overdose when mixed with opioids. Other substances, such as benzodiazepines and alcohol, can also increase the risk of opioid overdose.

In Hong Kong, there are 25 registered pharmaceutical products containing gabapentin, and 49 products containing pregabalin. All products are prescription-only medicines. As on 8 October 2019, the DH has received ADR related to gabapentin (3 cases) and pregabalin (9 cases), but these cases are not related to drug interaction.

Related news on concomitant use of gabapentin and opioids was previously issued by the MHRA, and was reported in the Drug News Issue No. 96.

The DH issued a letter to inform local healthcare professionals to draw their attention on 27 October 2017. In December 2017, the Registration Committee discussed the matter, and decided that warnings on central nervous system depression, sedation and respiratory depression with the concomitant use of gabapentin and opioids should be included in gabapentin-containing products. In light of the above Health Canada's announcement, the DH issued a letter to inform local healthcare professionals to draw their attention on 18 September 2019. The DH will remain vigilant on safety update of the drugs issued by other overseas drug regulatory authorities.

**UK: Montelukast (Singulair): reminder of the risk of neuropsychiatric reactions**

On 19 September 2019, the MHRA reminded prescribers that they should be alert for neuropsychiatric reactions in patients taking montelukast and carefully consider the benefits and risks of continuing treatment if they occur.

It has been known for some time that neuropsychiatric reactions may occur in association with montelukast treatment, and these reactions are listed as possible side effects in the product information in the UK. A recent European Union (EU) review confirmed the known risks of neuropsychiatric reactions and found that the magnitude of risk was unchanged. However, the review identified some cases in which there had been a delay in neuropsychiatric reactions being recognised as a possible ADR.

A range of neuropsychiatric reactions has been reported in association with montelukast. Among these are: sleep disturbances, depression and agitation (may affect up to 1 in 100 people taking montelukast); disturbances of attention or memory (up to 1 in 1,000 people); and very rarely, hallucinations and suicidal behaviour (up to 1 in 10,000 people).

In the UK, between 2014 and 2018, the MHRA received 219 reports of suspected adverse neuropsychiatric reactions to the Yellow Card Scheme, during which time there were approximately 14 million prescriptions of montelukast. Since montelukast was first marketed in the UK, the MHRA has received 639 reports of suspected adverse neuropsychiatric reactions. In the UK, the most frequently reported suspected neuropsychiatric reactions associated with montelukast have been nightmares/night terrors, depression, insomnia, aggression, anxiety and abnormal behaviour or changes in behaviour. These events were reported in all age groups. However, nightmare/night terrors, aggression, and behaviour changes are more frequently reported in the paediatric population.

The EU review also evaluated very rare reports of cases of speech impairment (dysphemia), described as 'stuttering'. Most of the cases were reported in children younger than 5 years, occurred shortly after montelukast was started (median time to onset 8 days) and sometimes occurred in conjunction with other suspected neuropsychiatric events. Where information was provided, in most cases the events resolved on stopping treatment.

In addition, the EU review endorsed the inclusion in the product information of very rare reports of obsessive-compulsive symptoms in the product information. Cases of obsessive-compulsive symptoms were reported to generally occur after a longer treatment period (median time to onset of 61 days) and sometimes occurred in conjunction with other neuropsychiatric events. Where information was provided, in most cases the events resolved on stopping treatment.

The product information in the UK is being updated to include stuttering and obsessive-compulsive symptoms as very rare (thought to affect fewer than 1 in 10,000 patients) potential neuropsychiatric adverse events with montelukast.

Healthcare professionals are advised:

- Be alert for neuropsychiatric reactions in patients taking montelukast; events have been reported in adults, adolescents, and children.
- Advise patients and their caregivers to read carefully the list of neuropsychiatric reactions in the patient information leaflet and seek medical advice immediately should they occur.
- Evaluate carefully the risks and benefits of continuing treatment if neuropsychiatric

reactions occur.
- Be aware of newly recognised neuropsychiatric reactions of speech impairment (stuttering) and obsessive-compulsive symptoms.

Patients and caregivers are advised:
- It is important that the patient or his/her child does not stop montelukast without talking to a doctor or asthma nurse first.
- Adverse reactions affecting sleep, behaviour, and mood have been infrequently reported in people taking montelukast.
- Always read the leaflet that accompanies their or their child's medicines, and talk to a healthcare professional if they suspect any serious reactions to montelukast.

In Hong Kong, there are 52 registered pharmaceutical products containing montelukast, and are prescription-only medicines. As on 8 October 2019, the DH has received 3 cases of ADR related to montelukast, of which one case was related to neuropsychiatric reactions, including speech disorder (strange speech). Related news was previously issued by the US FDA, Australia Therapeutic Goods Administration (TGA), Taiwan Food and Drug Administration (TFDA). Neuropsychiatric adverse effects of montelukast are documented in reputable drug references such as Martindale: The Complete Drug Reference. In light of the newly recognized neuropsychiatric reactions of speech impairment and obsessive-compulsive symptoms in the above MHRA's announcement, the DH issued a letter to inform local healthcare professionals to draw their attention on 20 September 2019, and the matter will be discussed by the Registration Committee.

# Drug Recall

**DH endorsed batch recall of Colchicine Tablets 0.5mg (HK-60077)**

On 10 September 2019, the DH endorsed a licensed drug wholesaler, Welldone Pharmaceuticals Limited (Welldone), to recall one batch (batch number: CCE802) of Colchicine Tablets 0.5mg (both packs of 100 tablets and 1000 tablets) (HK-60077) from the market due to a potential quality issue.

The DH received notification from Welldone on 10 September 2019 that one of the manufacturing processes of the affected batch manufactured in Taiwan was found not to be in compliance with the Good Manufacturing Practice requirements. Even though the finished product complied with the specifications, the manufacturer is recalling the affected batch as a precautionary measure. The DH noted that the recall was completed.

The above product, containing colchicine, is a prescription medicine used for the treatment of gout. According to Welldone, the affected batch of product has been supplied to local private doctors and pharmacies. Some products were also re-exported to Macao.

As on 8 October 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 10 September 2019 to alert the public of the product recall.

**DH endorsed recall of Zantac products**

On 24 September 2019, the DH endorsed a licensed drug wholesaler, GlaxoSmithKline Ltd (GSK), to recall all Zantac products from the market as a precautionary measure due to the presence of an impurity in the products.

The affected products are:
- Zantac Tablet 150mg (HK-42792)
- Zantac Tablet 300mg (HK-42793)
- Zantac Syrup 150mg/10ml (HK-30459)
- Zantac Injection 25mg/ml (HK-42045)

The DH received notification from GSK on 24 September 2019 that an impurity, *N*-nitrosodimethylamine (NDMA), was found in Zantac products by overseas regulatory authorities. NDMA is classified as a probable human carcinogen based on results from laboratory tests. GSK reported that the products' active ingredient, ranitidine, produced by an Indian manufacturer was found to contain low levels of NDMA. As a precautionary measure, GSK voluntarily has

recalled all Zantac products with the affected active ingredient from the market.

The DH, via its surveillance system, was aware that certain ranitidine-containing products were found to contain NDMA in other countries. The DH also noted that overseas drug regulatory authorities including the US FDA and the EMA have been reviewing the safety impact of the impurity found in the ranitidine-containing products, and will closely monitor 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. The DH issued a letter to notify local healthcare professionals about the issue on 18 September 2019.

The above products are medicines used for the treatment of gastric diseases. Oral preparations are over-the-counter medicines. According to GSK, the affected products have been supplied to the Hospital Authority, DH clinics, private hospitals, local private doctors and pharmacies. Some products were also re-exported to Macao.

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

As on 8 October 2019, the DH has not received any case of ADR in connection with the products. Press release was posted on the Drug Office website on 24 September 2019 to alert the public of the products recall.

## DH endorsed recall of three ranitidine-containing products

On 25 September 2019, the DH endorsed licensed drug wholesalers Hind Wing Co Ltd (Hind Wing) and Top Harvest Pharmaceuticals Co Ltd (Top Harvest) to recall three ranitidine-containing products from the market as a precautionary measure due to the potential presence of an impurity in the products.

The affected products are:

| Wholesaler | Product | Hong Kong Registration Number |
|---|---|---|
| Hind Wing Co Ltd | APO-Ranitidine Tablets 150mg | HK-42273 |
| | APO-Ranitidine Tablets 300mg | HK-41873 |
| Top Harvest Pharmaceuticals Co Ltd | Zantidon Tablets 150mg | HK-64329 |

The DH received notifications from Hind Wing and Top Harvest on 25 September 2019 that the manufacturers of the products are concerned about the potential presence of an impurity, NDMA, in the products. NDMA is classified as a probable human carcinogen based on results from laboratory tests. As a precautionary measure, both Hind Wing and Top Harvest have voluntarily recalled their affected products from the market.

The DH, via its surveillance system, was aware that certain ranitidine-containing products were found to contain NDMA in other countries. The DH also noted that overseas drug regulatory authorities including the US FDA and the EMA have been reviewing the safety impact of the impurity found in the ranitidine-containing products, and will closely monitor 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. The DH issued a letter to notify local healthcare professionals about the issue on 18 September 2019.

The above products are over-the-counter medicines used for the treatment of gastric diseases. According to Hind Wing, the affected products have been supplied to private hospitals, local private doctors and pharmacies. Some products were also re-exported to Macao. According to Top Harvest, the affected product has been supplied to local pharmacies.

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

As on 8 October 2019, the DH has not received any case of ADR in connection with the products. Press release was posted on the Drug Office website on 25 September 2019 to alert the public of the products recall.

## DH endorsed recall of two ranitidine-containing products

On 27 September 2019, the DH endorsed licensed drug manufacturer APT Pharma Limited (APT) and licensed drug wholesaler Eugenpharm International Limited (Eugenpharm) to recall their ranitidine-containing products from the market as a precautionary measure due to the presence of an impurity in the products.

The affected products are:

| Supplier | Product | Hong Kong Registration Number |
|---|---|---|
| APT Pharma Limited | Amratidine tablets 150mg | HK-53143 |
| Eugenpharm International Limited | Peptil H 150 tablets 150mg | HK-65103 |

The DH, via its surveillance system, was aware that certain ranitidine-containing products were found to contain NDMA in other countries and had been collecting samples of ranitidine-containing products from the market for analysis. The DH also noted that overseas drug regulatory authorities including the US FDA and the EMA have been reviewing the safety impact of the impurity found in the ranitidine-containing products. The DH will closely monitor 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. The DH issued a letter to notify local healthcare professionals about the issue on 18 September 2019.

Based on the DH's follow-up actions, samples of the above Amratidine tablets 150mg were collected for analysis and test results from the Government Laboratory confirmed that the samples contain low levels of NDMA. NDMA is classified as a probable human carcinogen based on results from laboratory tests. The potential risks are only associated with long-term exposure. In addition, Eugenpharm suspected that its Peptil H 150 tablets 150mg may also contain NDMA due to recent recalls of ranitidine-containing products. As a precautionary measure, both APT and Eugenpharm voluntarily recalled the affected products from the market.

The above products are over-the-counter medicines used for the treatment of gastric diseases. According to APT, the affected product has been supplied to the Hospital Authority, DH clinics, local private doctors, dentists, pharmacies and medicine companies, and some has been exported to Macao. On the other hand, Eugenpharm indicated that the affected product has been supplied to local pharmacies and medicine companies.

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

As on 8 October 2019, the DH has not received any case of ADR in connection with the products. Press release was posted on the Drug Office website on 27 September 2019 to alert the public of the products recall.

## DH endorsed recall of Weidos Tablets 150mg (HK-62210)

On 30 September 2019, the DH endorsed a licensed drug wholesaler, Vast Resources Pharmaceutical Limited (Vast Resources), to recall a ranitidine-containing product, namely Weidos Tablets 150mg (HK-62210), from the market due to the presence of an impurity in the product.

The DH received notification from Vast Resources on 30 September 2019 that the product's active ingredient was found to contain low levels of NDMA. NDMA is classified as a probable human carcinogen based on results from laboratory tests. As a precautionary measure, Vast Resources voluntarily recalled the affected product from the market.

The DH, via its surveillance system, was aware that certain ranitidine-containing products were found to contain NDMA in other countries and had been collecting samples of ranitidine-containing

products from the market for analysis. The DH also noted that overseas drug regulatory authorities including the US FDA and the EMA have been reviewing the safety impact of the impurity found in the ranitidine-containing products. The DH will closely monitor 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. The DH issued a letter to notify local healthcare professionals about the issue on 18 September 2019.

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

Patients who are taking 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 8 October 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 30 September 2019 to alert the public of the product recall.

**Overall situation related to detection of NDMA in ranitidine**

As on 8 October 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 8 October 2019, the DH has not received any case of ADR related to ranitidine.

Related news on the detection of *N*-nitrosodimethylamine (NDMA) in ranitidine products was previously issued by the EMA, the US FDA, Health Canada, Singapore HSA, Australia TGA, the TFDA and Macau Health Bureau. 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, GSK, to recall all Zantac products (HK-42792, HK-42793, HK-30459, HK-42045) from the Hong Kong market as a precautionary measure due to the presence of NDMA in the products.
- On 25 September 2019, the DH endorsed licensed drug wholesalers Hind Wing and Top Harvest 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 and licensed drug wholesaler Eugenpharm 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 to recall Weidos Tablets 150mg (HK-62210).

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.

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:** ***Pharmacovigilance Unit,***
***Drug Office, Department of Health,***
***Rm 1856, 18/F, Wu Chung House,***
***213 Queen's Road East,***
***Wan Chai, 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.***