Drug News
藥 物 情 報

Issue Number 126

This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in April 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: Chloroquine and hydroxychloroquine can have serious side effects. These drugs should be used only under the supervision of a physician.

On 25 April 2020, Health Canada announced that chloroquine and hydroxychloroquine may cause serious side effects, including serious heart rhythm problems. The risk of these side effects may increase at higher doses, or if the drugs are used in combination with other drugs, such as the antibiotic azithromycin. Patients should use these drugs only under the supervision of a physician. Health Canada is concerned that some people may be directly buying and using chloroquine and hydroxychloroquine to prevent or treat Coronavirus Disease 2019 (COVID-19) without a prescription.

Chloroquine and hydroxychloroquine are prescription medications approved in Canada to treat malaria and certain autoimmune diseases, including lupus and rheumatoid arthritis. They are known to potentially cause liver or kidney problems, low blood sugar (hypoglycemia) and nervous system problems such as dizziness, fainting, or seizures. The effects on heart rhythm, which in the most serious cases, may be fatal. Children are especially sensitive to these drugs, and even small doses taken by children can be dangerous.

Health Canada has not authorized any drugs to prevent, treat or cure COVID-19 and has warned Canadians about products making false and misleading claims. Health Canada has authorized clinical trials with chloroquine or hydroxychloroquine for COVID-19. Results from large, well-designed studies are essential to determine if the benefits of chloroquine and hydroxychloroquine outweigh their risks in the treatment of COVID-19. As on 25 April 2020, data from clinical trials are limited, and the results have not conclusively shown that any specific medications are effective against COVID-19. Health Canada will continue to closely monitor the safety and effectiveness of chloroquine, hydroxychloroquine, and other drugs used in the treatment of COVID-19. It will take appropriate and timely action if new health risks are identified, and inform Canadians as necessary.

Patients are advised:

- Use chloroquine or hydroxychloroquine only if it has been prescribed for them by a physician who is supervising their treatment.
- Contact their physician if they experience an irregular heart rate, dizziness, fainting, seizures, or other side effects while taking these drugs.
- Be cautious when buying drugs over the internet. If they have questions about whether an internet pharmacy is legitimate, contact the pharmacy regulatory authority in their province or territory.
- Report any health product adverse events.
- Report any complaints regarding unauthorized products.

Healthcare professionals are advised:

- Investigational use of approved therapies like hydroxychloroquine and chloroquine should be done in the context of a well-designed clinical trial.
- Consult the Canadian product monographs for a full list of contraindications, warnings and precautions, adverse reactions and drug interactions.
- Monitor patients closely if treated with chloroquine or hydroxychloroquine, especially if there are pre-existing heart conditions, when using higher doses, and if prescribing in combination with other medications such as

azithromycin that may prolong the QT interval.

In Hong Kong, there are 5 registered pharmaceutical products containing hydroxychloroquine, and all products are prescription-only medicines. There is no registered pharmaceutical product containing chloroquine. As on 5 May 2020, the Department of Health (DH) has received 4 cases of adverse drug reaction (ADR) related to hydroxychloroquine, but these cases are not related to heart rhythm problems, seizures or hypoglycaemia. The DH has not received any case of ADR related to chloroquine.

Related news on the risk of serious side effects (such as heart rhythm problems, seizures, hypoglycaemia, liver and kidney problems) associated with the use of chloroquine and hydroxychloroquine was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 62. The DH issued a letter to inform local healthcare professionals to draw their attention on risk of hypoglycaemia on 29 December 2014. In February 2015, the Registration Committee of the Pharmacy and Poisons Board (Registration Committee) discussed the matter, and decided that the sales pack labels or package inserts of chloroquine and hydroxychloroquine products should include the relevant risk of hypoglycaemia.

Adverse effects and precautions about heart rhythm problems, seizures, hypoglycaemia, hepatic and renal impairment associated with the use of chloroquine and hydroxychloroquine are 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.

EU: Suspension of ranitidine medicines in the EU

On 30 April 2020, the European Medicines Agency (EMA) of the European Union (EU) announced that its human medicines committee, the Committee for Medicinal Products for Human Use (CHMP), has recommended the suspension of all ranitidine medicines in the EU due to the presence of low levels of an impurity called *N*-nitrosodimethylamine (NDMA). NDMA is classified as a probable human carcinogen (a substance that could cause cancer) based on animal studies. It is present in some foods and water supplies and is not expected to cause harm when ingested at very low levels.

Available safety data do not show that ranitidine increases the risk of cancer, and any possible risk is likely to be very low. However, NDMA has been found in several ranitidine medicines above levels considered acceptable, and there are unresolved questions about the source of the impurities. There is some evidence that NDMA may form from the degradation of ranitidine itself with increasing levels seen over its shelf life. It is not clear whether NDMA can also be formed from ranitidine inside the body. Some studies suggest that it can while others do not. Given the uncertainties, the CHMP has recommended a precautionary suspension of these medicines in the EU.

Ranitidine medicines are used for reducing levels of stomach acid in patients with conditions such as heartburn and stomach ulcers. Alternatives are available and patients should contact their healthcare professionals if they need advice about which medicine to take. Many ranitidine medicines have not been available in the EU for several months. This is because national authorities in the EU have recalled them as a precaution while the EMA review was ongoing. The EMA has also recommended conditions for lifting the suspension of ranitidine medicines, including requirements for companies to provide more data.

Since 2018, NDMA and similar compounds known as nitrosamines have been detected in a number of medicines, with the EU regulators taking action to identify possible sources of the impurities and set strict new requirements for manufacturers. The EMA will continue working with national authorities, the European Directorate for the Quality of Medicines & HealthCare (EDQM), the European Commission and international partners to make sure that effective measures are taken to prevent the presence of these impurities in medicines.

Information for patients:

- Ranitidine medicines are being suspended in the EU as a precaution because of the presence at low levels of an impurity called NDMA.
- Alternative medicines are available. Contact their doctor or pharmacist if they have any questions about which alternative to take.
- If they have been prescribed ranitidine, their doctor will advise them on an alternative.

Information for healthcare professionals:

- Ranitidine medicines are being suspended in the EU due to the presence of NDMA impurities.
- Although the exact source of the impurity in ranitidine is yet to be determined, it is possible that NDMA may form from the degradation of ranitidine even under normal storage conditions. Some studies indicated that ranitidine may cause additional endogenous NDMA formation by its degradation or metabolism in the gastro-intestinal tract, although other studies did not.
- Available clinical and epidemiological data do not show that ranitidine increases the risk of cancer.
- While ranitidine medicines are unavailable, advise patients on alternative medicines.
- Healthcare professionals should advise patients who need assistance, including those who have been taking ranitidine without a prescription, on how to treat or manage conditions such as heartburn and gastric ulcers.

As on 5 May 2020, there are 64 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 May 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 and 124. 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. As previously reported, the matter will be discussed by the Registration Committee 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.

EU: EMA recommendations on DPD testing prior to treatment with fluorouracil, capecitabine, tegafur and flucytosine

On 30 April 2020, the EMA announced that it has recommended that patients should be tested for the lack of the enzyme dihydropyrimidine dehydrogenase (DPD) before starting cancer treatment with fluorouracil given by injection or infusion (drip) or with the related medicines, capecitabine and tegafur. As treatment for severe fungal infections with flucytosine (another medicine related to fluorouracil) should not be delayed, testing patients for DPD deficiency before they start treatment is not required.

Patient who completely lack DPD must not be given any fluorouracil medicines. For patients with partial deficiency, the doctor may consider starting cancer treatment at lower doses than normal or stopping flucytosine treatment if severe side effects occur. These recommendations do not apply to fluorouracil medicines used on the skin for conditions such as actinic keratosis and warts, as only very low levels of the medicine are absorbed through the skin.

A significant proportion of the general population has a deficiency of DPD (up to 9% of the Caucasian population have low levels of a working DPD enzyme, and up to 0.5% completely lack the enzyme), which is needed to break down fluorouracil and the related medicines capecitabine, tegafur and flucytosine. As a result, following treatment with these medicines, fluorouracil can build up in their blood, leading to severe and life-threatening side effects such as neutropenia (low levels of neutrophils, a type of white blood cells needed to fight infection), neurotoxicity (damage to the nervous system), severe diarrhoea and stomatitis (inflammation of the lining of the mouth).

Patients can be tested for DPD deficiency by measuring the level of uracil (a substance broken down by DPD) in the blood, or by checking for the presence of certain mutations (changes) in the gene for DPD. Relevant clinical guidelines should be taken into consideration.

Information for patients:

Fluorouracil, capecitabine or tegafur

- Before starting cancer treatment with fluorouracil given by injection or infusion, capecitabine or tegafur, their doctor should do a test to check whether they have a working DPD enzyme.
- If they have a known complete lack of DPD, they will not be given these treatments as they will increase the risk of severe and life-threatening side effects.
- If they have a partial DPD deficiency, their doctor may start treatment at low doses, which can be increased if there are no serious side effects.
- If they know that they have a partial DPD deficiency or if they have a family member who has partial or complete DPD deficiency, talk to their doctor or pharmacist before taking these medicines.
- If they are using fluorouracil applied to the skin for conditions such as actinic keratosis and warts they do not need a DPD test, as the level of fluorouracil absorbed through the skin into the body is very low.
- If they have any questions about their treatment or about DPD testing, talk to their doctor or pharmacist.

Flucytosine

- Flucytosine is a medicine related to fluorouracil that is used to treat severe yeast and fungal infections, including some forms of meningitis (inflammation of the membranes that surround the brain and spinal cord).
- As flucytosine may have to be given urgently, pre-treatment DPD testing (which may take up to one week) is not required in order to avoid any delay in starting therapy.
- If they have a known complete DPD deficiency they must not be given flucytosine,

due to the risk of life-threatening side effects.
- In case of side effects, their doctor may consider stopping treatment with flucytosine. Their doctor may also consider testing DPD activity, since the risk of severe side effects is higher in patients with a low DPD activity.
- If they have any questions about their treatment or about DPD testing, speak to their doctor.

Information for healthcare professionals:

Fluorouracil, capecitabine and tegafur

- Patients with partial or complete DPD deficiency are at increased risk of severe toxicity during treatment with fluoropyrimidines (fluorouracil, capecitabine, tegafur). Phenotype and/or genotype testing is therefore recommended before starting treatment with fluoropyrimidines.
- Treatment with fluorouracil, capecitabine or tegafur-containing medicines is contraindicated in patients with known complete DPD deficiency.
- A reduced starting dose should be considered in patients with identified partial DPD deficiency.
- Therapeutic drug monitoring of fluorouracil may improve clinical outcomes in patients receiving continuous fluorouracil infusions.

Flucytosine

- Pre-treatment testing for DPD deficiency is not required, in order to avoid delay in starting treatment with flucytosine.
- Treatment with flucytosine is contraindicated in patients with known complete DPD deficiency due to the risk of life-threatening toxicity.
- In case of drug toxicity, consideration should be given to stopping treatment with flucytosine. Determination of DPD activity may be considered where drug toxicity is confirmed or suspected.

The review was first carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which made a set of recommendations. The PRAC recommendations were sent to the CHMP, responsible for questions concerning medicines for human use, which adopted the Agency's opinion. The CHMP opinion will now be forwarded to the European Commission, which will issue a final legally binding decision applicable in all EU Member States in due course.

In Hong Kong, there are 4 registered pharmaceutical products containing fluorouracil, 24 products containing capecitabine and 4 products containing tegafur. All products are prescription-only medicines. There is no registered pharmaceutical product containing flucytosine. As on 5 May 2020, the DH has received 91 cases of ADR related to fluorouracil, 53 cases related to capecitabine (of which one case is related to dihydropyrimidine dehydrogenase deficiency) and 1 case related to tegafur. The DH has not received any case of ADR related to flucytosine.

Related news was previously issued by the EMA, and was reported in the Drug News Issue No. 113 and 125. The DH issued a letter to inform local healthcare professionals to draw their attention on 18 March 2019.As previously reported, the matter will be discussed by the Registration Committee.

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

Under the Import and Export Ordinance (Cap. 60), pharmaceutical products must be imported or exported under and in accordance with an import or export licence issued under the Import and Export Ordinance. Illegal import or export of pharmaceutical products are offences under the Import and Export Ordinance (Cap. 60) and the maximum penalty is a fine of $500,000 and 2 years' imprisonment.

Update on Drug Office's website: You can now search the newly registered medicines in the past year at http://www.drugoffice.gov.hk/eps/drug/newsNRM60/en/healthcare_providers?pageNoRequested=1.

Details of ALL registered pharmaceutical products can still be found in the Drug Office website at http://www.drugoffice.gov.hk/eps/do/en/healthcare_providers/news_informations/reListRPP_index.html.

Useful Contact

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