Drug News
藥 物 情 報

Issue Number 123

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

Australia: Medicines: Suspensions of ranitidine-containing products from the ARTG

On 8 January 2020, the Therapeutic Goods Administration (TGA) of Australia announced that 74 ranitidine-containing products from the following companies will be suspended from the Australian Register of Therapeutic Goods (ARTG) starting from 28 January 2020 for 6 months to 28 July 2020:

- Medis Pharma Pty Ltd
- Johnson & Johnson Pacific Pty Ltd
- Sandoz Pty Ltd
- Arrow Pharma Pty Ltd.
- Aspen Pharmacare Australia Pty Ltd
- Cipla Australia Pty Ltd
- Apotex Pty Ltd
- Medreich Australia Pty Ltd
- AFT Pharmaceuticals Pty Ltd
- Generic Health Pty Ltd
- Symbion Pty Ltd
- Orion Laboratories Pty Ltd T/A Perrigo Australia
- Nova Pharmaceuticals Australasia Pty Ltd
- Pharmacor Pty Ltd
- Soul Pattinson Manufacturing Pty Ltd
- Avallon Pharmaceuticals Pty Ltd
- Alphapharm Pty Ltd

Please refer to the website in the TGA for details of the affected products. The products will be suspended because under subsection 29D(1)(b); it is likely there are grounds for cancelling these medicines from the ARTG under section 30(2)(a) on the basis that the quality of the goods is unacceptable.

The following ranitidine products are registered pharmaceutical products in Hong Kong:

- Ranital Tab 150mg (HK-34755; a Sandoz product currently not available for sale) registered by Novartis Pharmaceuticals (HK) Limited.
- Zantac Syrup 150mg/10ml (HK-30459), Zantac Tab 75mg (HK-41114; currently not available for sale), Zantac Tab 150mg (HK-42792), Zantac Tab 300mg (HK-42793) and Zantac Inj 25mg/ml (HK-42045) registered by GlaxoSmithKline Limited.
- Apo-Ranitidine Tab 150mg (HK-42273) and Apo-Ranitidine Tab 300mg (HK-41873) registered by Hind Wing Co Ltd.
- Ulticer Tab 150mg (HK-53488) and Ulticer Tab 300mg (HK-52986; currently not available for sale) registered by Medreich Far East Limited.

The other products mentioned in the news are not registered pharmaceutical products.

As on 5 February 2020, there are 67 registered pharmaceutical products containing ranitidine in Hong Kong. These products in the forms of oral preparations and injections are controlled as over-the-counter medicines and prescription-only medicines respectively. As on 5 February 2020, the Department of Health (DH) has not received any case of adverse drug reaction (ADR) related to ranitidine.

Related news on the detection of *N*-nitrosodimethylamine (NDMA) in ranitidine products was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 122. The DH issued a letter to inform local healthcare professionals to draw their attention on 18 September 2019. The DH has contacted the relevant overseas drug regulatory authorities for further information regarding the detection of NDMA in ranitidine products, and continues to remain vigilant on the update findings and investigation result announced by the authorities for consideration of any action deemed

necessary.

The DH has contacted the certificate holders of all registered ranitidine products for follow up on the local impact of the issue; and to provide evidence that NDMA in the products are below the acceptable limit, and samples of ranitidine-containing products have been collected from the market for analysis. When any health risks are posed to the public, a press statement will be issued as soon as possible. Please find update information at Drug Office's website (www.drugoffice.gov.hk). The following are the main content of the press statements issued previously:

- On 24 September 2019, the DH endorsed a licensed drug wholesaler, GlaxoSmithKline Ltd, to recall all Zantac products (HK-42792, HK-42793, HK-30459, HK-42045) from the Hong Kong market as a precautionary measure due to the presence of NDMA in the products.
- On 25 September 2019, the DH endorsed licensed drug wholesalers Hind Wing 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 5 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. 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.

UK: Ondansetron: small increased risk of oral clefts following use in the first 12 weeks of pregnancy

On 27 January 2020, the Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom (UK) announced that recent epidemiological studies suggest exposure to ondansetron during the first trimester of pregnancy is associated with a small increased risk of the baby having a cleft lip and/or cleft palate.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. There is a growing body of evidence on the use of ondansetron in pregnancy that does not suggest an increase in the risk of overall congenital malformations combined.

Recent epidemiological studies report a small increased risk of orofacial malformations in babies born to women who used ondansetron in early pregnancy. Key evidence was an observational study of 1.8 million pregnancies in the United States of America (USA) of which 88,467 (4.9%) were exposed to oral ondansetron during the first trimester of pregnancy. The study reported that ondansetron use was associated with an additional 3 oral clefts per 10,000 births (14 cases per 10,000

births versus 11 cases per 10,000 births in the unexposed population). These data were recently reviewed within Europe and considered to be robust. As for all licensed medicines, the safety of ondansetron will be continuously monitored by the MHRA and relevant emerging information will be considered as it becomes available.

Outside of its authorised indications, ondansetron is also used second line for treating women with hyperemesis gravidarum, a severe and potentially life-threatening condition. If a physician considers, based on their professional judgement, the available evidence and the risks for mother and baby of malnutrition in early pregnancy, that a licensed treatment (for example doxylamine/pyridoxine, Xonvea) is not suitable or not sufficient alone to control severe nausea and vomiting in pregnancy, and there is a special clinical need to use ondansetron, then this decision should be made in consultation with the patient after she has been fully informed of the potential benefits and risks of the different treatment options. Prescribers should refer to clinical guidance if treatment with ondansetron is considered for severe nausea and vomiting in pregnancy.

Detailed findings of studies include a retrospective cohort study of a medical claims database in the USA included 1,816,414 pregnancies between 2000 and 2013, of which 88,467 (4.9%) were associated with a prescription of ondansetron during the first trimester. Exposure to ondansetron during the first 12 weeks of pregnancy was linked with a small but statistically significant increased risk of orofacial cleft defects (adjusted relative risk [aRR] 1.24, 95% CI 1.03–1.48).

A case-control study of another United States (US) medical claims database included 864,083 mother-infant pairs seen between 2000 and 2014, and found a non-statistically significant trend towards an increased risk of orofacial cleft defects in babies exposed to ondansetron compared with those not exposed to any antiemetic (adjusted odds ratio [OR] 1.30, 95% CI 0.75–2.25). This study also linked ondansetron use during the first trimester with an increased risk of cardiac defects (adjusted OR 1.43, 95% CI 1.28–1.61). However, this finding conflicts with results from other studies. For example, Huybrechts and colleagues did not find a significant association for cardiac defects after adjusting for pre-defined confounding factors (aRR 0.99, 95% CI 0.93–1.06).

The recent observational studies have some limitations inherent to the data sources, but the findings are considered sufficiently robust to indicate that use of ondansetron during the first trimester of pregnancy is associated with a small increased risk of the baby having a cleft lip and/or cleft palate.

If the clinical decision is to offer ondansetron in pregnancy, women must be counselled on the potential benefits and risks of use, both to her and to her unborn baby and the final decision should be made jointly.

In Hong Kong, there are 28 registered pharmaceutical products containing ondansetron. All products are prescription-only medicines. As on 5 February 2020, the DH has received 3 cases of ADR related to ondansetron, but these cases are not related to oral clefts in babies born to women who used ondansetron in early pregnancy. In light of the above MHRA's announcement, the DH issued a letter to inform local healthcare professionals to draw their attention on 29 January 2020. The DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

Drug Incident

Woman arrested for suspected illegal sale of unregistered pharmaceutical product

On 15 January 2020, the DH conducted an operation against the sale of an unregistered pharmaceutical product, during which a 25-year-old woman was arrested by the Police for illegal sale of an unregistered pharmaceutical product and a Part 1 poison.

Acting upon a public complaint, a medicinal patch labelled in Japanese as containing felbinac, a Part 1 poison under the Pharmacy and Poisons Ordinance (Cap. 138), was found being offered for sale via a social media platform. The operation revealed that the product label does not bear a Hong Kong pharmaceutical product registration number.

Felbinac is a non-steroidal anti-inflammatory drug used topically to relieve pain. It should only be used under the advice of healthcare professionals and be supplied at pharmacies under the

supervision of a registered pharmacist. Inappropriate use of felbinac may cause erythema and dermatitis.

People who have purchased the above product should stop using it and consult healthcare professionals for advice if in doubt or feeling unwell after use. Press release was posted on the Drug Office website on 15 January 2020 to alert the public of the drug incident.

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

All registered pharmaceutical products should carry a Hong Kong registration number on the package in the format of "HK-XXXXX". The products mentioned in the above incidents were not registered pharmaceutical products under the Ordinance in Hong Kong. Their safety, quality and efficacy cannot be guaranteed. Members of the public were exhorted not to use products of unknown or doubtful composition. They should stop using the aforementioned products immediately if they had them in their possession and to consult healthcare professionals if they felt unwell after taking the products. The products should be destroyed or disposed properly, or submitted to the Department's Drug Office during office hours.

Update on Drug Office's website: You can now search the newly registered medicines in the past year at http://www.drugoffice.gov.hk/eps/drug/newsNRM60/en/healthcare_providers?pageNoRequested=1.
Details of ALL registered pharmaceutical products can still be found in the Drug Office website at http://www.drugoffice.gov.hk/eps/do/en/healthcare_providers/news_informations/reListRPP_index.html.

Useful Contact

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The purpose of Drug News is to provide healthcare professionals with a summary of local and overseas drug safety news released. Healthcare professionals are advised to keep update with the information and provide corresponding advice or therapeutic measure to patients and public.