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(IN REPLY PLEASE QUOTE THIS FILE REF.)

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Dear Healthcare Professionals,

FDA requests removal of all ranitidine products (Zantac) from the market

Your attention is drawn to the US Food and Drug Administration's (FDA) announcement that it is requesting manufacturers withdraw all prescription and over-the-counter (OTC) ranitidine drugs from the market immediately. This is the latest step in an ongoing investigation of a contaminant known as N-nitrosodimethylamine (NDMA) in ranitidine medications (commonly known by the brand name Zantac). The agency has determined that the impurity in some ranitidine products increases over time and when stored at higher than room temperatures and may result in consumer exposure to unacceptable levels of this impurity. As a result of this immediate market withdrawal request, ranitidine products will not be available for new or existing prescriptions or OTC use in the United States.

The FDA did not observe unacceptable levels of NDMA in many of the samples that it tested. However, since the FDA does not know how or for how long the product might have been stored, the FDA decided that it should not be available to consumers and patients unless its quality can be assured.

NDMA is a probable human carcinogen (a substance that could cause cancer). In the summer of 2019, the FDA became aware of independent laboratory testing that found NDMA in ranitidine. Low levels of NDMA are commonly ingested in the diet, for example NDMA is present in foods and in water. These low levels would not be expected to lead to an increase in the risk of cancer. However, sustained higher levels of exposure may increase the risk of cancer in humans. The FDA conducted thorough laboratory tests and found NDMA in ranitidine at low levels. At the time, the agency did not have enough scientific evidence to recommend whether individuals should continue or stop taking ranitidine medicines, and continued its investigation and warned the public in Sep 2019 of the potential risks and to consider alternative OTC and prescription treatments.

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New FDA testing and evaluation prompted by information from third-party laboratories confirmed that NDMA levels increase in ranitidine even under normal storage conditions, and NDMA has been found to increase significantly in samples stored at higher temperatures, including temperatures the product may be exposed to during distribution and handling by consumers. The testing also showed that the older a ranitidine product is, or the longer the length of time since it was manufactured, the greater the level of NDMA. These conditions may raise the level of NDMA in the ranitidine product above the acceptable daily intake limit.

The FDA is sending letters to all manufacturers of ranitidine requesting they withdraw their products from the market. The FDA is also advising consumers taking OTC ranitidine to stop taking any tablets or liquid they currently have, dispose of them properly and not buy more; for those who wish to continue treating their condition, they should consider using other approved OTC products. Patients taking prescription ranitidine should speak with their health care professional about other treatment options before stopping the medicine, as there are multiple drugs approved for the same or similar uses as ranitidine that do not carry the same risks from NDMA. To date, the FDA's testing has not found NDMA in famotidine (Pepcid), cimetidine (Tagamet), esomeprazole (Nexium), lansoprazole (Prevacid) or omeprazole (Prilosec).

Please refer to the following website in FDA for details:

<https://www.fda.gov/news-events/press-announcements/fda-requests-removal-all-ranitidine-products-zantac-market>

Currently, 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. So far, the Department of Health (DH) has not received any case of adverse drug reaction related to ranitidine.

Related news on the detection of NDMA in ranitidine products was previously issued by various overseas drug regulatory authorities, and was posted on the Drug Office website since 16 Sep 2019, with the latest update posted on 28 Feb 2020. Letters to inform local healthcare professionals were issued by the DH on 18 Sep 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.

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. The following are the main content of the press statements issued previously:

- On 24 Sep 2019, the DH endorsed a licensed drug wholesaler, GlaxoSmithKline Ltd, to recall all Zantac

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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 Sep 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 Sep 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 Sep 2019, the DH endorsed licensed drug wholesaler Vast Resources Pharmaceutical Limited to recall Weidos Tablets 150mg (HK-62210).
- On 11 Oct 2019, the DH endorsed licensed drug wholesaler Hind Wing Co Ltd to recall Epadoren Solution for Injection 50mg/2ml (HK-61752).
- On 1 Nov 2019, the DH endorsed licensed drug wholesaler Welldone Pharmaceuticals Limited to recall 6 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 Nov 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 Nov 2019, the DH endorsed registration certificate holder Medreich Far East Limited to recall Ulticer Tab 150mg (HK-53488).
- On 27 Nov 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.

In light of the above FDA's announcement, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board for consideration of any action deemed necessary. Healthcare professionals are advised to balance the risk of possible adverse effects against the benefit of treatment.

Please report any adverse events caused by drugs to the Undesirable Medical Advertisements and Adverse Drug Reaction Unit of the DH (tel. no.: 2319 2920, fax: 2319 6319 or email: adr@dh.gov.hk). For details, please refer to the website at Drug Office under "ADR Reporting": <http://www.drugoffice.gov.hk/adr.html>. You may wish to visit the Drug Office's website for subscription and browsing of "Drug News" which is a monthly digest of drug safety news and information issued by Drug Office.

Yours faithfully,



(Joseph LEE)

for Assistant Director (Drug)

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