DRUG SAFETY INFORMATION No.66

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Health Products Regulation Group
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Dear Healthcare Professional

RETAIL-LEVEL RECALL OF EIGHT BRANDS OF RANITIDINE PRODUCTS FOUND TO CONTAIN N-NITROSODIMETHYLAMINE (NDMA)

The Health Sciences Authority (HSA) would like to inform healthcare professionals about the retail-level recall of eight brands of ranitidine products detected to contain trace amounts of N-nitrosodimethylamine (NDMA) that exceeded internationally acceptable level. Please refer to Table A for the list of recalled ranitidine products.

Table A. List of recalled ranitidine-containing products

	Product name	**Local supplier**
1	Aciloc 150 Tablet 150 mg Aciloc 300 Tablet 300 mg	Uni Drug House
2	Apo-Ranitidine Tablet 150 mg	Pharmaforte Singapore Pte Ltd
3	Hyzan Tablet 150 mg	Apex Pharma Marketing Pte Ltd
4	Neoceptin R-150 Tablet 150 mg	Pharmatech Resources (FE) Pte Ltd
5	Vesyca Film Coated Tablet 150 mg	Yung Shin Pharmaceutical (Singapore) Pte Ltd
6	Xanidine Tablet 150 mg	Polymedic Trading Enterprise Pte Ltd
7	Zantac Injection 25 mg/ml Zantac Syrup 150 mg/10 ml Zantac Tablet 150 mg	GlaxoSmithKline Pte Ltd
8	Zynol-150 Tablet 150 mg	Naina Mohamed & Sons Private Limited

Background

2 Ranitidine belongs to the class of H_2-antagonists and is indicated for the treatment of gastrointestinal disorders including reflux oesophagitis, duodenal ulcer, benign gastric ulcer, post-operative ulcer and Zollinger-Ellison Syndrome. It is a prescription only medicine but may be supplied without a doctor's prescription by pharmacists for up to 14 days for the short-term relief of heartburn, dyspepsia and hyperacidity.

3 Since June 2018, several angiotensin II receptor blockers (ARBs) were recalled globally due to the presence of nitrosamine impurities. HSA has been working with international regulators and companies to investigate the possible causes of the contamination. As part of the investigations, HSA and other regulators have also been testing other non-ARB medicines for the presence of nitrosamines. It was recently discovered that NDMA could be present in medicines containing the active ingredient ranitidine.

4 HSA tested all locally marketed ranitidine products and NDMA was detected above internationally acceptable level in all these ranitidine products except for one ranitidine injection (Gastril injection by Duopharma (Singapore) Pte Ltd). To date, nitrosamines have not been detected in other H_2-antagonists, i.e., famotidine and cimetidine.

HSA's Benefit-Risk Assessment

5 Nitrosamine impurities are potential human carcinogens based on carcinogenic effects observed in animal studies. The potential risk of cancer is with long-term exposure to unacceptable levels of the impurities. Nitrosamine compounds can also be found in very small quantities in certain food products (e.g. pickled vegetables, salted fish and processed meat products) and tobacco products.

6 The presence of carcinogenic impurities is generally unacceptable in medicines, unless in unavoidable circumstances. In these instances, stringent limits are set based on international harmonised guidelines. The internationally acceptable daily intake level is determined based on a cancer risk of 1 in 100,000 for exposure over a lifetime (i.e. over 70 years).

7 The amount of NDMA detected in the affected ranitidine products are in trace amounts, which exceeded the acceptable level of 96 ng/day. As the potential risks are associated with long term exposure, patients prescribed the affected ranitidine products may continue with their medicines.

8 HSA is directing the companies to stop the sales of the affected ranitidine products and recall them from the clinics, hospitals and pharmacies. This will limit patients' further exposure to such products. In the meantime, HSA is working with international regulatory agencies and companies marketing ranitidine products to verify the causes of the contamination, and to formulate the measures to address the issue.

Advisory

9 Healthcare professionals are advised to:

- stop prescribing or dispensing the above affected ranitidine products
- return the remaining stocks to the respective companies
- review the treatment options for patients who may require ranitidine medicine on a longer term
- prescribe other suitable alternatives as all ranitidine products (with the exception of Gastril Injection) are being recalled

10 For enquiries on product returns of the recalled products, please refer to Annex B.

11 HSA will continue to communicate any relevant updates and findings on the local situation to healthcare professionals. Further clarifications can be made through the HSA hotline at 6866-1111 or email at hsa_productsafety@hsa.gov.sg.

Thank you.

Yours faithfully

MS JALENE POH
DIRECTOR
VIGILANCE AND COMPLIANCE BRANCH
HEALTH PRODUCTS REGULATION GROUP
HEALTH SCIENCES AUTHORITY

cc Director of Medical Services, Ministry of Health

ANNEX A Frequently Asked Questions

Why are these impurities only found in the ranitidine medicines now?

Contamination of medicines with nitrosamine impurities is a new and evolving issue. HSA has been working with international regulatory authorities to identify the root causes of the contamination in affected medicines and the measures to address the issue.

HSA and other international regulatory agencies have also been testing other medicines for the presence of nitrosamines as part of the investigation. It was recently discovered that NDMA could be present in medicines containing the active ingredient, ranitidine. HSA immediately prioritised the investigation and testing of ranitidine products that are available in Singapore.

Why is the recall conducted at retail level and not consumer level?

HSA has assessed that ranitidine is generally prescribed for short term use, unlike in the previous recall which involved losartan, a long-term medicine used to control high blood pressure. As the potential risks with nitrosamines are associated with long term exposure, HSA is conducting a retail level recall and not a consumer level recall.

What is the cancer risk to patients who have been taking the affected products for 2-4 weeks?

Nitrosamine compounds are also found in very small quantities in certain food products (e.g. pickled vegetables, salted fish and processed meat products) and tobacco products.

The excess cancer risk for taking 4 weeks' treatment of ranitidine products with the highest level of NDMA detected is estimated to be 0.00003%.

ANNEX B

Table B: Contact numbers of local suppliers

	Product name	Local supplier	Contact number
1	Aciloc 150 Tablet 150 mg Aciloc 300 Tablet 300 mg	Uni Drug House	68484229
2	Apo-Ranitidine Tablet 150 mg	Pharmaforte Singapore Pte Ltd	64528488
3	Hyzan Tablet 150 mg	Apex Pharma Marketing Pte Ltd	67413803
4	Neoceptin R-150 Tablet 150 mg	Pharmatech Resources (FE) Pte Ltd	62846636
5	Vesyca Film Coated Tablet 150 mg	Yung Shin Pharmaceutical (Singapore) Pte Ltd	67412466
6	Xanidine Tablet 150 mg	Polymedic Trading Enterprise Pte Ltd	62836826
7	Zantac Injection 25 mg/ml Zantac Syrup 150 mg/10 ml Zantac Tablet 150 mg	GlaxoSmithKline Pte Ltd	65313030
8	Zynol-150 Tablet 150 mg	Naina Mohamed & Sons Private Limited	67416455