

4 December 2019

Health Products Regulation Group
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Dear Healthcare Professional

RECALL OF THREE METFORMIN PRODUCTS FOUND TO CONTAIN N-NITROSODIMETHYLAMINE (NDMA)

The Health Sciences Authority (HSA) would like to inform healthcare professionals about the consumer-level recall of three metformin products, which HSA has detected to contain trace amounts of N-nitrosodimethylamine (NDMA) beyond the internationally acceptable level. HSA has tested all the metformin products in the Singapore market, and found that besides these three products, none of the other 43 metformin products contain NDMA above the acceptable level. Please refer to Table A for the list of recalled metformin products.

Table A. List of the recalled metformin-containing products

	Product name	Batch recalled	Local supplier
1	Glucient XR Extended-release tablet 500 mg	One batch: 2881382	Glorious Dexa Singapore
2	Meijumet Prolonged Release Tablet 750Mg	All batches	Pharmazen Medical Pte Ltd
3	Meijumet Prolonged Release Tablet 1000Mg	All batches	Pharmazen Medical Pte Ltd

*Refer to Annex A for the list of other metformin products that have been tested and are not affected by this recall.

Background

2 Metformin is used for the treatment of type 2 diabetes mellitus, particularly in overweight patients, when dietary management and exercise are unable to achieve adequate glycaemic control.

3 Since June 2018, several angiotensin II receptor blockers (ARBs) were recalled globally due to the presence of nitrosamine impurities. The detection of nitrosamine was unexpected, and is a regulatory concern because nitrosamine impurities are potential human carcinogens. Regulators have undertaken many recalls worldwide for affected ARBs with such impurities above the international acceptable levels. Subsequently, nitrosamine impurities were also detected in ranitidine products.

4 It was recently discovered that NDMA could be present in medicines containing the active ingredient metformin. HSA has tested all metformin products that are marketed locally, i.e. single-ingredient and combination-ingredient products. NDMA above the internationally acceptable level was detected in three single-ingredient metformin products available in Singapore. The 21 other single-ingredient metformin products and 22 metformin combination products do not contain NDMA above the acceptable level. Please refer to Annex A.

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 (70 years).

7 The NDMA detected in the affected metformin products are in trace amounts beyond the acceptable level of 96 ng/day¹, and are being recalled. The potential risks are however associated with long-term exposure. The three affected medicines have only been supplied locally for only a short period of time since 2018, hence the risk to patients is very low.

8 HSA is working with international regulatory agencies and companies marketing metformin products to verify the causes of the contamination and to formulate the necessary measures to address the issue.

Advisory

9 Healthcare professionals are advised to:

- stop prescribing or dispensing the above affected metformin products;
- contact patients who have been prescribed the affected metformin medicines as soon as practicable to return to the clinic for an exchange of unaffected medicines or suitable alternatives;
- return the remaining stocks of these affected products to the respective companies.

10 HSA will be publishing this information on our website to advise patients taking the affected products not to stop taking the medicines on their own until they have seen their doctor and have been provided with alternative medicines. 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 6866-3538 or email at hsa_productsafety@hsa.gov.sg.

Yours faithfully



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DIRECTOR
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cc Director of Medical Services, Ministry of Health

¹ The excess cancer risk from an additional 6-month exposure is estimated to be less than 0.00002%.

ANNEX A**Table 1. List of metformin products (single ingredient) unaffected by recall**

	Products	Local Supplier
1	Auro Metformin 500 Film-Coated Tablets 500 Mg Bp	Novartis (Singapore) Pte Ltd
2	Auro Metformin 850 Film-Coated Tablets 850 Mg Bp	Novartis (Singapore) Pte Ltd
3	Diabetmin Tablet 500 Mg	Goldplus Universal Pte Ltd
4	Diabetmin Xr Tablet 500mg	Goldplus Universal Pte Ltd
5	Diabetmin Tablet 850mg	Goldplus Universal Pte Ltd
6	Diamet Tablet 500 Mg	Singapore Pharmaceutical Private Limited
7	Glucomet Tablet 500mg	Yung Shin Pharmaceutical (Singapore) Pte Ltd
8	Glucophage Tablet 850 Mg	Merck Pte Ltd
9	Glucophage Tablet 1000 Mg	Merck Pte Ltd
10	Glucophage Xr 500 Mg Extended Release Tablet	Merck Pte Ltd
11	Glucophage Xr 750mg Extended Release Tablet	Merck Pte Ltd
12	Glucophage Xr 1000mg Extended Release Tablet	Merck Pte Ltd
13	Glycomet Tablet 500 Mg	Zyfas Medical Co
14	Glycomet-850 Tablet 850 Mg	Zyfas Medical Co
15	Glyformin 500 Tablet 500 Mg	Goldplus Universal Pte Ltd
16	Metformin Tablet 500 Mg	Beacons Pharmaceuticals Pte Ltd
17	Metformin Tablets 250 Mg	Beacons Pharmaceuticals Pte Ltd
18	Metformin Tablet 500 Mg	Pharmatech Resources (Fe) Pte Ltd
19	Metformin Tablet 250 Mg (Film-Coated)	Sunward Pharmaceutical Private Limited
20	Metformin Tablet 500 Mg	Sunward Pharmaceutical Private Limited
21	Metformin 850 Tablet 850mg	Sunward Pharmaceutical Private Limited

Table 2. List of metformin products (combination ingredients) unaffected by recall

	Product Name	Local Supplier
1	Galvus Met Tablet 50mg/1000mg	Novartis (Singapore) Pte Ltd
2	Galvus Met Tablet 50mg/850mg	Novartis (Singapore) Pte Ltd
3	Galvus Met Tablet 50mg/500mg	Novartis (Singapore) Pte Ltd
4	Glucovance Tablet 500 Mg/5 Mg	Merck Pte. Ltd.
5	Janumet™ Tablet 50mg/500mg	MSD Pharma (Singapore) Pte. Ltd.
6	Janumet™ Tablet 50mg/850mg	MSD Pharma (Singapore) Pte. Ltd.
7	Janumet™ Tablet 50mg/1000mg	MSD Pharma (Singapore) Pte. Ltd.
8	Janumet Xr Tablet 50mg/500mg	MSD Pharma (Singapore) Pte. Ltd.
9	Janumet Xr Tablet 50mg/1000mg	MSD Pharma (Singapore) Pte. Ltd.
10	Janumet Xr Tablet 100mg/1000mg	MSD Pharma (Singapore) Pte. Ltd.
11	Jardiance Duo Film Coated Tablet 12.5mg/1000mg	Boehringer Ingelheim Singapore Pte. Ltd.
12	Jardiance Duo Film Coated Tablet 12.5mg/850mg	Boehringer Ingelheim Singapore Pte. Ltd.
13	Jardiance Duo Film Coated Tablet 12.5mg/500mg	Boehringer Ingelheim Singapore Pte. Ltd.
14	Jardiance Duo Film Coated Tablet 5mg/500mg	Boehringer Ingelheim Singapore Pte. Ltd.
15	Kombiglyze Xr Tablet 2.5mg/1000mg	Astrazeneca Singapore Pte Ltd
16	Kombiglyze Xr Tablet 5mg/1000mg	Astrazeneca Singapore Pte Ltd
17	Trajenta Duo Film-Coated Tablets 2.5mg / 500mg	Boehringer Ingelheim Singapore Pte. Ltd.
18	Trajenta Duo Film-Coated Tablets 2.5mg /850mg	Boehringer Ingelheim Singapore Pte. Ltd.
19	Trajenta Duo Film-Coated Tablets 2.5mg / 1000mg	Boehringer Ingelheim Singapore Pte. Ltd.
20	Xigduo Xr Tablets 5mg/500mg	Astrazeneca Singapore Pte Ltd
21	Xigduo Xr Tablets 10mg/1000mg	Astrazeneca Singapore Pte Ltd
22	Xigduo Xr Tablets 5mg/1000mg	Astrazeneca Singapore Pte Ltd

ANNEX B

Table 1: Contact numbers of local suppliers

	Product name	Batch recalled	Local supplier	Contact number
1	Glucient XR Extended-release tablet 500 mg	One batch: 2881382	Glorious Dexa Singapore	6760 3588
2	Meijumet Prolonged Release Tablet 750Mg Meijumet Prolonged Release Tablet 1000Mg	All batches	Pharmazen Medical Pte Ltd	6743 2017

ANNEX C

Frequently Asked Questions

1. Should patients taking these affected medicines stop taking them immediately?

Sudden stopping of these medicines can pose greater health risks to patients than the contamination with NDMA, whose risks are associated with long-term exposure. However, as the levels of NDMA in the three metformin products have exceeded the interim acceptable level, patients should have their treatment options reviewed by their doctor and be prescribed with suitable alternative products.

2. What is the cancer risk to patients who have been taking the affected products for a few months?

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 from an additional 6-month exposure to metformin products with the highest level of NDMA detected is estimated to be less than 0.00002% (or 1 in 5 million).

3. Why are these impurities only found in the metformin medicines now?

Contamination of medicines with nitrosamine impurities was unexpected, and is a recent 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 reviewing the risk of nitrosamine contamination in other medicines as part of the investigation. It was recently discovered that NDMA could be present in medicines containing the active ingredient, metformin. HSA immediately prioritised the investigation and testing of metformin products that are available in Singapore.