South African Health Products
Regulatory Authority
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COMMUNIQUE

COMMUNICATION TO INDUSTRY ON THE RANITIDINE-CONTAINING MEDICINES THAT ARE REGISTERED AND IN PROCESS IN SOUTH AFRICA

To: All applicants

From: PEM Unit Manager

Date: 12 October 2020

The South African Health Products Regulatory Authority (SAHPRA), in collaboration with other regulatory agencies, are reviewing all ranitidine-containing medicines with the following Active Pharmaceutical Ingredient; ranitidine. SAHPRA previously issued a media release regarding the recall and quarantine of ranitidine containing medicines (29 October 2019 and 20 January 2020).

This encompassing review was triggered with respect to the potential formation of N-nitrosamine impurities i.e. N-nitrosodimethylamine (NDMA) during the manufacturing process of the above mentioned Active Pharmaceutical Ingredients (APIs). NDMA are classified probable human carcinogens (a substance capable of causing cancer) and mutagens (a substance capable of causing a permanent change in an organism's genetic make-up), based on the results from laboratory tests.

Although the exact source of the impurity is yet to be determined, it is possible that NDMA may form from the degradation of ranitidine, even after normal storage conditions.

SAHPRA is currently reviewing the levels of NDMA and any other N-nitrosamine impurities in these ranitidine-containing medicines and the measures that can be taken to reduce or eliminate the impurity from future batches produced by companies.

Below are queries from the Pharmaceutical Evaluations & Management unit for your attention and response regarding the ranitidine-containing medicines which are in process or registered. Companies are requested to take note, that the response to these queries should be submitted no later than six **(6) months** after the date of this notification for registered and all new applications for ranitidine-containing medicines.

General

1. In your response, ensure that the code **VRR – RANITIDINE – APPLICANT NAME** is indicated as the folder name and on the cover letter.

2. State the valid CEP or current DMF number used during the application.

Module 3.2.S.2

3. Each registration holder should conduct a thorough review of the manufacturing process (es) of the "ranitidine" APIs used in their finished products with respect to the potential formation of N-nitrosamines during the manufacturing process (e.g. N-nitrosodimethylamine (NDMA).

3.1 The exact source of the impurity is yet to be determined during the synthesis of ranitidine. However, the registration holder should discuss the potential for formation of N-nitrosamines and provide a detailed description of the relevant process steps including quench, work-up, phase separation and extraction procedures, as well as information on waste streams. If information is considered confidential, such information can be submitted directly to SAHPRA by the API manufacturer making reference to affected final pharmaceutical product proprietary name and application or registration number.

3.2 In the discussion, include the types of amine compounds used (primary, secondary or tertiary) since there is a potential for generation of N-nitrosamines when a secondary amine is present in the reaction mixture under acidic conditions and when a nitrite salt is used. Secondary amines could originate from impurities in or degradants of solvents (e.g. DMF - dimethylformamide, DMA - dimethylacetamide, NMP - N-Methyl-2-pyrrolidone) or reagents (e.g. tertiary amine bases such as Et_3N, etc.), or be present intentionally, e.g. as part of a raw material.

3.3 State if you are currently using (or have previously used) any API supplier that has steps in the API manufacturing process that may potentially lead, or have led, to the generation of NDMA or any other possible N-nitroso impurities.

Module 3.2.S.4.1

4. Provide the revised signed, dated and version controlled specifications by the API and FPP manufacturers which should include the control of the N-nitrosamine impurities.

Module 3.2.S.4.3

5. The API manufacturer should preferably use analytical methods used by European Official Medicines Control Laboratories (OMCLs). If a manufacturer prefers to use other methods, then full details of the analytical methods, including the method validation should be provided. See link below;

https://www.edqm.eu/sites/default/files/medias/fichiers/OMCL/omcl_cvua_karlsruhe_method_for_determination_of_nitrosamines_in_ranitidine_-_25102019.pdf

Alternatively, you can use the analytical methods established by the USFDA. See links below;

https://www.fda.gov/media/130801/download

https://www.fda.gov/media/131868/download

6. Submit validation data for forced degradation studies of the API. A specific and quantitative validated method for related substance, described in full, should be used in these studies. Supporting chromatograms, where relevant, should be included in the methods or validation section.

Module 3.2.S.4.4

7. Provide CoAs and batch analysis data on three consecutive recently manufactured batches on the levels of NDMA and any other N-nitrosamine impurity in the manufactured API and finished product(s).

8. Below are the tentative limits for the impurity:

	NDMA	
Active substance (max daily dose)	**Maximum daily intake (ng)**	**Limit (ppm)**
Ranitidine (300 mg)	96.0	0.320

Below are the maximum daily intake limits for other nitrosamine impurities:

Active substance (max daily dose)	**Name of Nitrosamine impurity**	**Allowable daily intake (ng/day)**
NDMA	N-nitrosodimethylamine	96.0
NDEA	N-nitrosodiethylamine	26.5
NMPA	N-nitroso-N-methyl-propylamine	26.5
NMBA	N-nitroso-N-methyl-4-aminobutyric acid	96.0
DIPNA	N-nitrosodiisopropylamine	26.5
EIPNA	N-nitrosoethylisopropylamine	26.5

Module 3.2.S.7.3

9. Provide a summary of the results of the stress testing studies should be provided including the treatment conditions (e.g., concentrations of solutions prepared, storage temperatures and durations) and the observations for the various test parameters (e.g., assay, degradation products) as well as a discussion of the results (e.g., observance of mass balance, potential impact on drug product manufacture, likelihood of formation of impurities under accelerated and long term conditions). This should confirm the absence or low detection of the NDMA impurity.

10. Submit stability data which include the control of NDMA for batches that have been placed under stability, to confirm the absence or low detection of the NDMA impurity.

Module 3.2.P.2

11. Drug product manufacturers should conduct risk assessments to determine the potential for nitrosamine impurities in drug products. A risk assessment should involve collaboration with the API manufacturer to aid in the identification of the API route of synthesis (ROS) or other process conditions of the API's manufacture that put the drug product at risk for nitrosamine impurities. The risk assessment should also include evaluation of any pathway (including degradation) that may introduce nitrosamines during drug product manufacture or storage. If the risk assessment determines that there is no potential for nitrosamine impurities, there is no need to take further action.

Module 3.2.P.3.3

12. If a nitrosamine impurity is detected, manufacturers should investigate the root cause and implement changes in the manufacturing process to mitigate or reduce nitrosamine impurities.

Module 3.2.P.5.1

13. If a nitrosamine impurity is detected above the LOQ, the manufacturer should develop a strategy to ensure that the nitrosamine level remains within the allowable intake limit. The control strategy should include specification limits for the identified nitrosamines. This should be accompanied by CoAs and batch analysis data on three consecutive production batches.

Module 3.2.P.5.3

14. If a risk of nitrosamines in a drug product is identified through detection, confirmatory testing of batches should be conducted using sensitive and appropriately validated methods.

Module 3.2.P.5.4

15. Provide CoAs and batch analysis data on three consecutive production batches on the levels of NDMA/NDEA and any other N-nitrosamine impurities in the final pharmaceutical product(s).

Module 3.2.P.8.3

16. Provide stability data or a commitment to place at least one production batch on stability to confirm that the nitrosamine impurities are not formed over time in the final product.

For submission of the response, you are required to upload the document into SAHPRA's File transfer Protocol (FTP) server. For more information and to request access to this document upload system please contact newmedicines@sahpra.org.za. A copy of these queries and the amendment schedule must be included in your response.

Issued by:

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About SAHPRA

SAHPRA is tasked with regulating (monitoring, evaluating, investigating, inspecting and registering) all health products and clinical trials in South Africa. Health products include complementary medicines, medical devices and in vitro diagnostics (IVDs). SAHPRA also has the responsibility of overseeing the radiation control in South Africa. SAHPRA's mandate is outlined in the Medicines and Related Substances Act (Act No 101 of 1965 as amended) as well as the Hazardous Substances Act (Act No 15 of 1973).

SAHPRA has three pillars to ensure that medicines, medical devices and IVDs meet the requisite standards to protect the health and well-being of South Africans:

- Safety
- Efficacy
- Quality

It is these three pillars that define the ethos of SAHPRA.