South African Health Products
Regulatory Authority
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COMMUNIQUE

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

To: All applicants

From: PEM Unit Manager

Date: 12 October 2020

The notice of concern for the above registered products refers.

The South African Health Products Regulatory Authority (SAHPRA), in collaboration with other regulatory agencies, are reviewing all sartan-containing medicines with the following Active Pharmaceutical Ingredients; azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan and valsartan. SAHPRA previously issued a press release regarding the recall of Pharma Dynamics DynavalCo range, containing the active ingredient, valsartan (23 July 2018) and a follow-up re-assurance on the safety of valsartan containing medicines registered in South Africa (20 December 2018). A communication to industry has also been published titled: request to industry on the sartan-containing medicines that are in-process and registered in South Africa (06 August 2019).

This encompassing review was triggered with respect to the potential formation of N-nitrosamine impurities i.e. N-nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA) during the manufacturing process of the above mentioned Active Pharmaceutical Ingredients (APIs). NDMA and NDEA 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. The presence of these impurities appears to be generated during the formation of the tetrazole ring by reaction of dimethylamine (which may be present as an impurity or degradant in the solvent dimethylformamide (DMF) and sodium nitrite under acidic conditions where nitrous acid is formed.

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

Similar letters were sent to companies between August and September of 2019 after the August Communique. It is noted that you may have responded to the queries below regarding the sartan-containing medicines which are in process or registered. However, the Pharmaceutical Evaluations Unit has not been able to receive the response.

General

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

2. State the valid CEP or current DMF number as well as the API source used during the application.

Module 3.2.S.2

3. Each registration holder should conduct a thorough review or risk assessment of the manufacturing processes) of the "sartan" APIs used in their finished products with respect to the potential formation of N-nitrosamines during the manufacturing process (e.g. N-nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA)).

3.1 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. 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. In addition, submit specifications for all solvents, reagents and raw materials used in the manufacture of the API.

3.3 N-nitrosamines appear to be generated during the formation of the tetrazole ring by reaction of dimethylamine (which may be present as an impurity or degradant in the solvent (DMF)) and sodium nitrite under acidic conditions (where nitrous acid is formed). State whether a nitrite salt is used in the process.

3.4 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, NDEA or any other possible N-nitrosamine 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/en/news/omcls-release-three-methods-determination-ndma-sartans

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

   https://www.fda.gov/media/125478/download

   https://www.fda.gov/media/124025/download

   https://www.fda.gov/media/115965/download

   https://www.fda.gov/media/124025/download

   https://www.fda.gov/media/124025/download

Module 3.2.S.4.4

6. Provide CoAs and batch analysis data on three consecutive production batches on the levels of NDMA/NDEA and any other N-nitrosamine impurity in the manufactured API and finished product(s). Below are the tentative limits from EDQM and USFDA for the impurities:

EDQM:

	NDMA		NDEA	
Active substance (max daily dose)	**Maximum daily intake (ng)**	**Limit (ppm)**	**Maximum daily intake (ng)**	**Limit (ppm)**
Candesartan (32 mg)	96.0	3.000	26.5	0.820
Irbesartan (300 mg)	96.0	0.320	26.5	0.088
Losartan (150 mg)	96.0	0.640	26.5	0.177
Olmesartan (40 mg)	96.0	2.400	26.5	0.663
Valsartan (320 mg)	96.0	0.300	26.5	0.082

https://www.edqm.eu/en/news/update-edqm-review-cep-applications-sartan-substances-4-february-2019

USFDA:

Drug	**Maximum Daily Dose (mg/day)**	**Acceptable Intake NDMA (ng/day)***	**Acceptable Intake NDMA (ppm)****	**Acceptable Intake NDEA (ng/day)***	**Acceptable Intake NDEA (ppm)****	**Acceptable Intake NMBA (ng/day)***	**Acceptable Intake NMBA (ppm)****
Valsartan	320	96	0.3	26.5	0.083	96	0.3
Losartan	100	96	0.96	26.5	0.27	96	0.96

Irbesartan	300	96	0.32	26.5	0.088	96	0.32
Azilsartan	80	96	1.2	26.5	0.33	96	1.2
Olmesartan	40	96	2.4	26.5	0.66	96	2.4
Eprosartan	800	96	0.12	26.5	0.033	96	0.12
Candesartan	32	96	3.0	26.5	0.83	96	3.0
Telmisartan	80	96	1.2	26.5	0.33	96	1.2

* The acceptable intake is a daily exposure to a compound such as NDMA, NDEA, or NMBA that approximates a 1:100,000 cancer risk after 70 years exposure

** These values are based on a drug's maximum daily dose as reflected in the drug label

NMBA: N-Nitroso-N-methyl-4-aminobutyric acid

https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan

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.P.2

7. 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 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

8. 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

9. 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

10. 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

11. 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).

For products that are in-process the queries should be factored in during a response to recommendations. Applicants are given 1 (one) month to respond from the date in which they receive the letter notification. 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.

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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.