COMMUNIQUE

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

To all applicants

From: The Acting CEO of SAHPRA

Date: 25 July 2019

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).

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.

Below are queries from the Medicines Evaluation & Research unit for your attention and response regarding the sartan-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 sartan-containing medicines.

General

1. In your response, ensure that the code **VRR (sartans)** is indicated in 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 "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-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-nitrosomine 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

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-nitroso 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

Companies should kindly submit the response to these queries by (CD). A copy of these queries and the amendment schedule must be included in your response.

Portia Nkambule

Acting CEO: SAHPRA