MCAZ Medicines Control Authority of Zimbabwe

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CIRCULAR 10 of 2020

Date: 22 October 2020

To: All applicants and principals with products with the following Active Pharmaceutical Ingredients: Candesartan, Losartan, Irbesartan, Olmesartan and Valsartan.

RE: N-NITROSAMINE IMPURITIES IN ANGIOTENSIN II RECEPTOR BLOCKERS

Reference is made to the notifications by other regulatory agencies concerning the presence of previously undetected N-nitrosamine impurities in Angiotensin II Receptor Blockers (sartan-containing medicinal products) with a tetrazole ring. The synthesis process of these compounds has been shown to potentially lead to the formation of probable human carcinogens i.e. nitrosamine impurities. These impurities include but are not limited to N-nitrosodiethylamine (NDEA), nitrosodimethylamine (NDMA), 4-methyl nitrosoamino butanoic acid (NMBA), N-nitrosodiisopropylamine (DIPNA) and N-nitrosoethylisopropylamine (EIPNA).

Consequently, the Medicines Control Authority of Zimbabwe requires you to:

1. Conduct a thorough review of the routes of synthesis of the Active Pharmaceutical Ingredients (APIs) mentioned above with respect to the potential for formation of N-nitrosamine impurities. The review should take special note of solvents which can potentially result in formation of these impurities.
2. Conduct risk assessment to identify the causes of nitrosamine contamination and put in place limits to ensure control of such impurities below acceptable levels. Tentative limits as recommended by EMA should be considered. For nitrosamine impurities that have no published limits, the principles as outlined in ICH's M7 (R1) guideline are recommended to be used to determine acceptable levels.
3. Provide a detailed description of the relevant steps and measures used to mitigate the identified risk(s).
4. Revise Active Pharmaceutical Ingredient (API) specifications and analytical procedures of your product(s) to include tests and limits for nitrosamine impurities, as appropriate.
   Please be advised that analytical methods developed by European OMLS (see https://www.edqm.eu/en/ad-hoc-projects-omcl-network) or USFDA (see https://www.USFDA.gov/media/124025/download) should be considered. If other methods are used, details of the methods and full validation data demonstrating that the methods can detect the N-nitrosamine impurities should be provided.

Please note that the information on the risk assessment should be provided together with variation to the approved API specifications from both the API and FPP manufacturer.

The Authority is giving you up to the **30th of April 2021** to conduct the investigations, submit the necessary variation applications and comply with the tentative limits as per ICH M7 for potential genotoxic substances.

Yours faithfully,

MEDICINES CONTROL AUTHORITY OF ZIMBABWE

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G.N. MAHLANGU (Ms)
DIRECTOR-GENERAL