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Ref: 10/3/1

Date: 03 June 2019

OFFICE OF THE REGISTRAR OF MEDICINES

DEAR HEALTHCARE PROFESSIONAL

COMMUNICATION OF NITROSAMIDE IMPURITIES DETECTED IN SOME ANGIOTENSIN II RECEPTOR BLOCKER CONTAINING PRODUCTS

Background

In June 2018, the manufacturer of valsartan – Zhejiang Huahai Pharmaceuticals, Linhai (China) – notified the European Commission about an impurity known as N-nitrosodimethylamine (NDMA) that was found in their product, valsartan – the active pharmaceutical ingredient (API).

Following that, in July 2018, Pharma Dynamics recalled their valsartan-containing products, the Dynaval Co range from the Namibian market, as they sourced their active ingredient from the above mention pharmaceutical company. Similarly, a few other companies have made voluntary recalls of batches of angiotensin receptor blockers (ARBs) or sartan containing products that were found to contain nitrosamine impurities such as N-nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA).

Nitrosamines are probable human carcinogens that are known environmental contaminants found in water and foods, including meats, dairy products and vegetables. Risks assessments by the US FDA concluded that the maximum possible exposure to nitrosamines in sartan medicines appears to be small; nevertheless, their presence in drug products is not acceptable. While the goal is to have no quantifiable nitrosamine impurities in sartans, interim limits have been set for nitrosamines in line with current international guidelines.

The EU has tentatively recommended the limits in the table below:

	NDMA		NDEA	
API (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

Before June 2018, NDMA and NDEA were not detected among the impurities in the sartan medicines. It is now known that these impurities can form during the production of sartans that contain tetrazole. Tetrazole, in the presence of certain solvents, reagents, catalysts and other raw materials, these impurities are formed. In addition, it is possible that impurities were present in some sartans because manufacturers had inadvertently used contaminated equipment or reagents in the manufacturing process.

The European Medicines Agency (EMA) conducted an assessment to estimate the quantities of NDMA and NDEA in sartan medicines. They found that the vast majority of sartan medicines, did not contain these impurities and that those that had, had very low levels. Furthermore, EMA estimated the highest possible cancer risk with these impurities and concluded that the incidence of cancer would be 22 per 100,000 patients who took the highest dose of valsartan from Zhejiang Huahai pharmaceutical company (had highest levels of impurities in their products) for six years. In addition, EMA found that NDEA in these medicines could lead to eight cancer cases per 100,000 patients who took the highest dose of valsartan for four years. The EMA resolved that products containing either impurity above the set interim will not be allowed in the EU.

The transition period, which will last for 2 years, will allow companies to make the necessary changes to their manufacturing processes and to put in place testing regimes able to detect the smallest amounts of these impurities. After the transition period, companies must exclude the presence of even lower levels of NDEA or NDMA in their products (< 0.03 parts per million).

Recently, the US FDA announced that since the first nitrosamine case was discovered, have not found these impurities in 40 sartan medications. They concluded that the 40 medications they assessed do not contain any of these impurities.

They further indicated that removing the affected medications from the market has led to shortages. However, FDA found some losartan that contained nitrosamines at levels higher than the set allowable levels in the interim. After evaluating safety data and consideration of the benefits and risks to patients, the agency thought it is critical that patients have access to these medicines while impurity-free losartan is manufactured. Consequently, patients have been advised to continue taking their medicines until their pharmacist provides a replacement or their doctor provides an alternative treatment option even if they learn that their sartan medicine is recalled.

Action by the Namibia Medicines Regulatory Council (NMRC)

In ensuring that registered sartan products on the Namibian market do not have quantities of the impurities above the interim acceptable limits, the NMRC has actively engaged the manufacturers of the sartan active pharmaceutical ingredients (API) and final pharmaceutical product (FPP). Marketing Authorization Holders (MAHs) are given six months to conduct investigations and comply with the tentative limits. In response, they should submit variations for their API and FPP specifications. Products which do not comply will be recalled from the Namibian market.

The NMRC will provide more information on the outcome of the investigations and any regulatory actions taken. For the time being, health workers are encouraged to advise their patients who are receiving sartan medication to continue with their treatment.

Yours Sincerely,

MR. JOHANNES GAESEB
REGISTRAR OF MEDICINES