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Nitrosamine Impurities in Metformin-Containing Medicines: the Current Situation in Ukraine

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Introduction. In 2019–2020, global concern arose following the detection of N-nitrosodimethylamine (NDMA) in specific batches of metformin, prompting investigations and product recalls in numerous countries. These findings prompted national and international regulatory authorities, including the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), to conduct a series of investigations. As a result, many manufacturers took precautionary measures and voluntarily recalled the affected products. These recalls were based primarily on analytical results provided by regulatory authorities or independent laboratories that found NDMA levels exceeding the acceptable intake (AI) limits set by health authorities. The focus was mainly on metformin drugs in the form of extended-release (ER) tablets. Still, the situation with immediate-release (IR) tablets is almost not covered in official documents and scientific literature.

Materials and methods. The objects of the study were IR tablets containing 500 mg of metformin, manufactured by Ukrainian manufacturers (complete production cycle), Ukrainian manufacturers of tablets "in bulk" (primary and secondary packaging), and global manufacturers. The determination of nitrosamine impurities (N-nitrosodimethylamine NDMA, N-nitrosodiethylamine NDEA, N-nitrosodiisopropylamine NDIPA, N-nitrosodi-n-butylamine NDBA, N-nitrosoethylisopropylamine NEIPA, N-nitroso-N-methyl-4 -aminobutanoic acid NMBA) in IR tablets containing 500 mg of metformin was performed by liquid chromatography with mass spectrometric detection on the Agilent 1290 in accordance with the method included in the European Pharmacopoeia 11.0 (2.5.42).

Results and discussion. According to the data obtained, all samples tested exceeded the AI established by the FDA and EMA for the content of specific nitrosamines. Despite the fact that the results for tablets of different manufacturers vary significantly, all samples contained NDMA and NDEA impurities at concentrations that exceeded the established AI by several times. In addition, tablets of three manufacturers were found to exceed the NEIPA AI limit. Some samples also contained NMBA or NDBA impurities.

The results obtained allow us to conclude that, firstly, IR tablets of metformin may contain nitrosamine impurities, although the body of scientific and regulatory data mainly concerns ER dosage forms, and, secondly, metformin-containing drugs may be contaminated not only with NDMA, but also other small-molecule nitrosamines, most of which are considered to be more potent carcinogens and mutagens (for example, the established AI for NDMA is 96 ng/day, and for NDEA, NEIPA, NDBA, NDIPA – 26.5 ng/day).

Conclusions. Nitrosamine impurities in medicines, including metformin preparations, remain a serious challenge for the pharmaceutical industry. This situation requires further efforts to minimize the risk of nitrosamine contamination in metformin preparations, the implementation of stricter quality control measures, improvements in manufacturing practices, and the development of sensitive and reliable analytical methods for the detection and quantification of nitrosamine impurities in pharmaceutical preparations.