20 August 2019
EMA/351053/2019 rev 1

Temporary interim limits for NMBA, DIPNA and EIPNA impurities in sartan blood pressure medicines

The risks associated with the presence of the nitrosamines N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA) in sartan blood pressure medicines (angiotensin II receptor blockers) containing a tetrazole ring have been assessed in a referral under Article 31 of Directive 2001/83/EC within procedure EMEA/H/A-31/1471. Temporary interim limits based on the TD_{50} values in rat carcinogenicity studies have been set for NDMA and NDEA: acceptable intakes (AI) of 96.0 ng for NDMA and 26.5 ng for NDEA.

Potential contamination with other *N*-nitrosamines was also considered during this procedure. Such impurities could be generated if different sources of secondary or tertiary amine are present at the same time as nitrite. Some common organic solvents (e.g. *N*-methylpyrrolidone, which could give rise to 4-(methyl)(nitroso)amino)butanoic acid [NMBA]) and amine bases (e.g. diisopropylethylamine [DIPEA], which could give rise to *N*-nitrosodiisopropylamine [DIPNA) and N-nitrosoethylisopropylamine [EIPNA]) would present such risks. (NMBA has been detected in losartan batches of Hetero Labs. NMBA may also be referred to as BMSA, nitrosomethyl-3-carboxypropylamine and 4-(methylnitrosamino) butyric acid (MNBA).

The Safety Working Party (SWP) has critically assessed the available experimental toxicological data on NMBA, DIPNA and EIPNA. Only for NMBA and DIPNA could toxicological data be retrieved from public sources. For EIPNA no data have been found. The SWP considers the experimental toxicological data as insufficient to derive protective substance specific AI levels for NMBA, DIPNA and EIPNA. The carcinogenicity studies for NMBA and DIPNA do not provide appropriate numbers of dose groups or group size to calculate robust TD50 values. Mutagenicity data are also insufficient. The only conclusion that can be drawn is that NMBA and DIPNA are potent carcinogens in rats.

In line with the methodology suggested in ICH M7 chapter 7.5, carcinogenicity data from closely related structures may be used on a case-by-case basis. To identify closely related structures, an expert structure activity relationship analysis (SAR) was performed. This analysis suggested that NDMA and NDEA data could be used to derive AI levels for NMBA and also for DIPNA and EIPNA based on their close SAR and the alkyldiazonium ions formed. According to Sulc et al. (2010) alkyl N-nitrosamines are bio-transformed via α-hydroxylation with the release of carbonyl compounds such as formaldehyde to the corresponding alkyldiazonium ions being responsible for covalent modification of DNA.

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The SAR analyses provide plausible arguments for close relationship of NMBA to NDMA and of DIPNA/EIPNA to NDEA. The data of the most closely related compounds were used as a point of departure for calculation of AI levels. Based on the TD_{50} data for NDEA (for DIPNA and EIPNA) and NDMA (for NMBA) in rats, compound specific AI levels associated with a theoretical excess cancer risk of 1:100,000 when exposed daily for a lifetime have been calculated according to ICH M7 (R1). The limits are given in the table below together with corresponding parts per million (ppm) values in the maximum daily dose of each sartan.

Table 1. Acceptable Intake (AI) levels and corresponding concentrations of DIPNA, EIPNA and NMBA per active substance for their maximum daily dose authorised in the European Union.

API	Max. daily dose (mg)	DIPNA, EIPNA AI (ng/day)	DIPNA, EIPNA Corresponding concentration level (ppm in API)	NMBA AI (ng/day)	NMBA Corresponding concentration level (ppm in API)
Valsartan	320	26.5	0.082	96.0	0.300
Losartan	150	26.5	0.177	96.0	0.640
Olmesartan	40	26.5	0.663	96.0	2.400
Irbesartan	300	26.5	0.088	96.0	0.320
Candesartan	32	26.5	0.820	96.0	3.000

References

Sulc M, Hodek P, Stiborova M (2010). The binding affinity of carcinogenic *N*-nitrosodimethylamine and *N*-nitrosomethylaniline to cytochromes P450 2B4, 2E1 and 3A6 does not dictate the rate of their enzymatic N-demethylation. *Gen Physiol Biophys*. 29: 175–185