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Ref. EMP/RHT/Information Note_Nitrosamine impurities **20 Nov. 2019**

WHO Information Note

UPDATE ON NITROSAMINE IMPURITIES

Background

Medicine Regulatory Authorities first became aware of the presence of the nitrosamine impurity, *N*-nitrosodimethylamine (NDMA), in products containing valsartan in July 2018. Valsartan is an Angiotensin II Receptor Blocker (ARB) and belongs to a family of analogue compounds commonly referred to as the sartans.

Further nitrosamine impurities were subsequently detected in other medicines belonging to the sartan family, including: *N*-nitrosodiethylamine (NDEA), *N* -nitrosodiisopropylamine (NDIPA), *N* -nitroso-ethylisopropylamine (NEIPA) and *N* -nitroso-N-methyl-4-aminobutyric acid (NMBA).

More recently, nitrosamine impurities have been reported in pioglitazone and ranitidine containing products.[1-3]

What are nitrosamines?

Nitrosamines, or more correctly *N*-nitrosoamines, refer to any molecule containing the nitroso functional group. These molecules are of concern because nitrosamine impurities are probable human carcinogens. Although they are also present in some foods and drinking water supplies, their presence in medicines is nonetheless considered unacceptable.

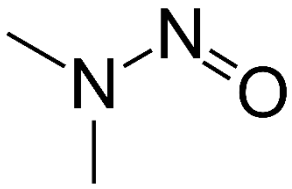

Figure 1: *N*- nitrosodimethylamine (NDMA)

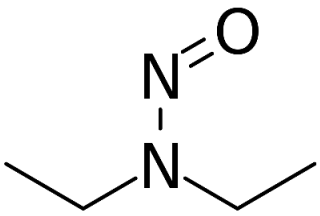

Figure 2: *N*-nitrosodiethylamine (NDEA)

Why are they present?

The formation of nitrosamines is generally only possible when secondary or tertiary amines react with nitrous acid. Nitrous acid itself is unstable but can be formed *in situ* from nitrites (NO_2) under acid conditions.

In the case of the sartan compounds, most contain a tetrazole ring and formation of this tetrazole ring employs the use of sodium nitrite. Coincidently the solvents employed either were amines, or contained traces of amines, and this likely afforded the observed NDMA and NDEA. The origins of NDMA content in batches of ranitidine currently remains unclear.

However, during on-going investigations it was also concluded that the possibility for nitrosamine impurity content was broader than simply the concurrent presence of nitrites and amines in the synthesis of the active pharmaceutical ingredient (API).[4]

Evidence suggests that sources of nitrites or amines as unintentional contaminants of starting materials, reagents and solvents – such as dimethylamine in the common solvent dimethyl formamide (DMF) – may also provide circumstances in which nitrosamines may form. The carryover of nitrites or amines from

subsequent steps may also afford opportunities for formation. _Notably, contamination from external sources has been identified as a source of nitrosamine content. In particular, contamination from the use of recycled materials and solvents that already contain levels of nitrosamines. A cited example of this involves the use of recycled DMF, which is quenched with sodium nitrite to destroy residual azide as part of the recovery process. Furthermore, the recycling of materials and solvents is often outsourced to third parties who may not implement adequate controls in view of the content of the materials they are processing. Materials and solvents can become cross-contaminated with nitrosamines or with impurities that could react downstream to form nitrosamines, if equipment is not adequately cleaned between customers. [4b]

Importantly, these additional mechanisms, in particular cross-contamination, are to varying degrees product non-specific and may affect products that would otherwise not be expected to be at risk of nitrosamine formation. These broader concerns have prompted the European Medicines Agency (EMA)[5] to request that Marketing Authorisation Holders (MAHs) of all Finished Pharmaceutical Products (FPPs) conduct risk assessment to determine the risk of nitrosamine content.

Toxicity

NDMA and NDEA belong to the so-called "cohort of concern", which is a group of highly potent mutagenic carcinogens that have been classified by the WHO's International Agency for Research on Cancer as probably human carcinogens. Despite the potency of these impurities, there is still a very low risk that nitrosamine impurities at the levels found could cause cancer in humans.

Only limited impurity-specific toxicity data is available for NDMA and NDEA. Based on this information interim acceptable intakes for these specific impurities have been adopted by most major regulators, as indicated in table 1.

Due to their structural similarity, NDIPA, NEIPA, and NMBA are considered by international regulators to exhibit a toxicological profile like NDMA and NDEA.

For a nitrosamine impurity that is not included in Table 1, the principles as outlined in ICH's M7(R1) guideline[8] are recommended to be used to determine an acceptable Intake. At least one nitrosamine analogue of valsartan proved to be Ames test negative.[4]

Table 1: Interim allowable daily intake limits for selection N-Nitrosamine impurities

Impurity name Abbreviation	Chemical name	Allowable Daily Intake (AI)
NDMA[6]	N-nitrosodimethylamine	96.0 ng/day
NDEA[6]	N-Nitrosodiethylamine	26.5 ng/day
NMBA[7]	N-Nitroso-N-methyl-4-aminobutyric acid	96.0 ng/day
DIPNA[7]	N-nitrosodiisopropylamine	26.5 ng/day
EIPNA[7]	N-nitrosoethylisopropylamine	26.5 ng/day

Regulatory Action

In the European Union (EU), following an Article 31 review of sartans at risk of containing nitrosamine impurities (those containing a tetrazole ring),[9] manufacturers were asked to review and make changes to their manufacturing processes to minimise nitrosamine impurities to the extent practically possible. A transition period of two years has been allowed to make these changes. During this transition period, interim limits as outlined in table 1 are being applied to products. Batches of product exceeding these limits for an individual impurity, or batches containing both NDMA and NDEA are not allowed in the EU.

Revisions are being made to the European Pharmacopoeia to the drug substances monographs for the sartan series to include testing for nitrosamines. In addition, the general monograph for APIs (General monograph 2034) is under revision and will also include appropriate tests.

As a result of these measures, multiple sartan products were temporarily recalled from the EU market. Many have now returned to market; however, EU advice to patients was not to stop their treatments unless they have been advised to do so by their pharmacist or doctor.

In a similar manner, the USFDA worked to identify and recall medicines with levels above interim acceptable limits. The USFDA publishes a list of ARB products and their status with respect to nitrosamine content.[10] Like the EMA, the USFDA emphasised that the risks (such as stroke) of abruptly discontinuing these drugs far outweigh the low risk associated with continuing the medications with these impurities.

More recently levels of the impurity NDMA has been detected in batches of ranitidine and nizatidine products. Ranitidine medicines are used widely to reduce the production of stomach acid in patients with conditions such as heartburn and stomach ulcers. They are available over-the-counter and on prescription.

Regulatory agency reactions have varied. Some individual European national regulators, as well as Swissmedic and Health Canada, took precautionary measures to either recall or suspend distribution of all ranitidine products until analysis of batches demonstrated NDMA was below acceptable levels. The EMA is currently evaluating available data to assess whether patients using ranitidine are at any risk from NDMA.[11]

Other authorities, such as the USFDA, have requested voluntary recall of products only if test results indicate levels of NDMA above the interim levels.[12] The USFDA has determined that the levels of NDMA observed in most ranitidine and nizatidine products are similar to levels expected if you ate common foods like grilled or smoked meats.

Many companies have initiated voluntary recalls of their ranitidine products as preventative measures.

As a general measure, the EMA has requested that the MAHs of all FPPs evaluate the possibility of nitrosamines being present in all products containing chemically-synthesize active ingredients.[5] Although nitrosamines are not expected to form during the manufacture of the vast majority of medicines, the possibility of cross contamination or unintentional introduction of amines and nitrites, has prompted the request for companies to undertake this precautionary review. These reviews are expected to be broad in scope and to consider all aspects of the manufacturing process including FPP manufacture. The EMA has requested that MAHs complete this review within 6 months.

Test methods

The low levels at which the nitrosamine impurities occur creates challenges for testing. To assist in the testing of samples the USFDA has published several test methods that may be considered when determining nitrosamine content in the API or FPP.

https://www.USFDA.gov/media/124025/download -
https://www.USFDA.gov/media/115965/download
https://www.USFDA.gov/media/130801/download
https://www.USFDA.gov/media/131868/download

The USFDA has recommend the use of an LC-HRMS method when testing ranitidine due to the lower temperate conditions of the method; higher temperature conditions of some test methods may cause the sample to generate NDMA.[13]

Similarly, the Official Medicines Control Laboratories (OMCLs) Network of the Council of Europe has also published several methods that may be used when testing for nitrosamines and is available at this web address – https://www.edqm.eu/en/ad-hoc-projects-omcl-network.

Recommendations

For sartan, ranitidine and other products, where nitrosamines content has been positively identified, Regulatory Agencies should be taking steps to:
verify the levels of nitrosamine in the products on their markets, whether using national testing laboratories or self-declarations from the suppliers themselves. Appropriate test methods should be used.
request the MAHs of these products undertake risk assessments to identify the causes of nitrosamine contamination and put in place limits to ensure control of such impurities below acceptable levels.
request MAHs undertake changes to ensure that the future levels of nitrosamines are essentially absent.

As an interim measure the values in table 1 represent the best available information regarding daily permitted intake. For other nitrosamine impurities not listed in table 1, the principles outlined in ICH's M7(R1) guideline[8] are recommended to be used to determine an acceptable Intake.

As a result of investigations into the presence of nitrosamines, it is apparent that a complete consideration of potential nitrosamine contamination in an FPP must be broader than whether sources of amines and nitrites are concurrently used in the preparation of the API. Manufacturers of all FPPs should be assessing their products for any circumstances that might inadvertently lead to nitrosamine content and taking steps to mitigate these risks. The EU request to manufacturers,[5] provides a detailed description of the factors that should be considered.

In cases where the level of a single nitrosamines impurity is observed below the interim acceptable limits, such products are generally considered safe and may remain on the market.

In cases where the levels of nitrosamines exceed acceptable limits, or more than one nitrosamine is observed, such products should in general not be permitted on the market. However, when considering this action, each national authority must also balance the impact on the patient if the product is no longer available. This involves determining the availability of alternative brands or treatments on their own market and the clinical impact of stopping or switching to a different treatment.

In all cases to-date, patients are being advised not to discontinue treatment unless at the advice of a health care professional.

WHO will continue to monitor the issue of nitrosamine contamination and provide updates as required. Attention should also be paid to the websites of the USFDA and EMA, where new information resulting from the ongoing investigations will be published.

References

1 https://www.ema.europa.eu/documents/press-release/update-nitrosamine-impurities-ema-continues-work-prevent-impurities-medicines_en.pdf
2 https://www.ema.europa.eu/en/news/ema-review-ranitidine-medicines-following-detection-ndma
3 https://www.USFDA.gov/news-events/press-announcements/statement-alerting-patients-and-health-care-professionals-ndma-found-samples-ranitidine
4 https://www.ema.europa.eu/en/documents/referral/sartans-article-31-referral-chmp-assessment-report_en.pdf
4b https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-information-nitrosamines-marketing-authorisation-holders_en.pdf
5 https://www.ema.europa.eu/en/news/ema-advises-companies-steps-take-avoid-nitrosamines-human-medicines
6 February 2019, EMA/44960/2019: Sartan medicines: companies to review manufacturing processes to avoid presence of nitrosamine impurities.
9 20 August 2019 EMA/351053/2019 rev 1: Temporary interim limits for NMBA, DIPNA and EIPNA impurities in sartan blood pressure medicines.
8 https://database.ich.org/sites/default/files/M7_R1_Guideline.pdf
9 https://www.ema.europa.eu/en/documents/referral/valsartan-article-31-referral-sartan-medicines-companies-review-manufacturing-processes-avoid_en.pdf
10 https://www.USFDA.gov/drugs/drug-safety-and-availability/USFDAs-assessment-currently-marketed-arb-drug-products
11 https://www.ema.europa.eu/en/medicines/human/referrals/ranitidine-containing-medicinal-products
12 https://www.USFDA.gov/drugs/drug-safety-and-availability/laboratory-tests-ranitidine.
13 https://www.USFDA.gov/drugs/drug-safety-and-availability/USFDA-updates-and-press-announcements-ndma-zantac-ranitidine