U.S. FOOD & DRUG ADMINISTRATION

Contains Nonbinding Recommendations

October 28, 2024: Emerging Scientific and Technical Information on Ritonavir

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations.

FDA is aware that a nitrosamine drug substance-related impurity, (*N*-((2-isopropylthiazol-4-yl)methyl)-*N*-methylnitrous amide (NITMA), also known as *N*-nitroso-2,4-thiazoleamine (NNTA), may be present in some finished drug products containing ritonavir. At this time, FDA has determined that an Acceptable Intake (AI) limit of 26.5 ng/day is recommended for NITMA, absent appropriate justification by an applicant for a higher limit.[1]

Nitrosamine drug substance-related impurities (NDSRIs) are a class of *N*-nitrosamine (nitrosamine) impurities sharing structural similarity to the active pharmaceutical ingredient (API) in drug products. (See FDA guidance for industry *Control of Nitrosamine Impurities in Human Drugs* (September 2024), *Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (NDSRIs)* (August 2023), *CDER Nitrosamine Impurity Acceptable Intake Limits* (October 2024)). FDA is informing manufacturers and applicants, including those with applications pending before the Agency, of ritonavir-containing products of FDA's concerns related to a nitrosamine impurity that may be in such drug products. Nitrosamine impurities contain a nitroso group which places them in the "cohort of concern" for highly potent mutagenic carcinogens as discussed in the M7(R2) guidance on DNA-reactive impurities. (See FDA guidance for industry *M7(R2) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* (July 2023)).

At this time, FDA considers that NITMA exposure at or below 26.5 ng/day would not pose a safety concern. Manufacturers and applicants may propose an alternative AI limit based on a safety assessment that considers mutagenicity and carcinogenicity. If a testing battery is warranted to evaluate mutagenic and carcinogenic potential, FDA recommends that manufacturers and applicants contact the appropriate review division within the Agency before initiating any studies. In the absence of an acceptable justification to support a higher limit, we recommend that manufacturers and applicants control NITMA such that exposure does not exceed the recommended AI limit of 26.5 ng/day.

[1] EMA identifies this impurity as *N*-nitroso-2,4-thiazoleamine (NNTA), with a recommended AI limit of 18 ng/day using the Carcinogenic Potency Categorization Approach (CPCA) method. For further information, see https://www.ema.europa.eu/en/documents/other/appendix-1-acceptable-intakes-established-n-nitrosamines_en.xlsx. For products intended for marketing in the United States, FDA recommends an AI limit of 26.5 ng/day for Category 1 of the CPCA, even if a different limit is recommended in other regulatory regions.

We recommend that manufacturers and applicants test their ritonavir drug products to determine whether they contain NITMA. If NITMA is detected, manufacturers and applicants should perform a root cause investigation to identify the source and take appropriate measures to reduce or prevent the formation of NITMA. As described in the FDA guidance for industry *Control of Nitrosamine Impurities in Human Drugs* (September 2024), if changes are necessary to prevent or reduce NITMA in approved drug products, manufacturers and applicants of approved drugs should report these changes to the Agency in accordance with 21 CFR 314.70 by August 1, 2025. Holders of pending applications should assess their products for this identified risk and inform FDA if confirmatory testing finds nitrosamine levels above the recommended AI limit. Prospective applicants should address NITMA in their NDA or ANDA before submission but can submit an amendment after filing if data are not available at the time of filing of the original submission. Contact the appropriate review division if you have questions.

Manufacturers and applicants of approved drugs considering an action that is likely to lead to a disruption in the supply of drugs produced at their facilities should contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov. Contacting the Drug Shortages Staff also allows manufacturers to meet any obligations to report discontinuances or interruptions in drug manufacture under section 506C of the FD&C Act and allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on these products.

Additionally, FDA generally does not intend to object to manufacturers and applicants distributing approved drug products containing NITMA in ritonavir while it investigates this issue. As FDA's understanding of the root cause of this issue evolves and potential practices that can remediate or eliminate this concern develop, the Agency may inform application holders of a recommended interim AI limit for these impurities.