

Nitrosamine concerns for rifapentine and rifampicin

Update and FAQs

What are nitrosamines?

Nitrosamines are possible human carcinogens. They may increase the risk of cancer if persons are exposed to them above acceptable levels and over long periods of time.

These impurities can be formed in some medicines during manufacturing under certain conditions. They can also be present because of contamination (e.g. from equipment, starting materials, reagents or solvents) or because of degradation. They are not expected in the vast majority of APIs and medicines. The formation of a nitrosamine impurity can be specific to the product or non-specific (for example, in the case of cross-contamination).

Nitrosamine impurities are also present in air, water, food and other products.

What if a nitrosamine impurity is detected in a medicine?

Nitrosamine impurities should be avoided in medicines, or at least controlled below a level where human cancer risk associated with the exposure is negligible.

If a nitrosamine impurity is detected in a medicine, the manufacturer needs to investigate the root cause and apply mitigation measures to avoid or minimize the exposure. Possible root causes for the formation of nitrosamines have been published recently by the European Medicines Agency and the U.S. Food and Drug Administration.

Mitigation measures may require investigation, and changes to the product. These measures may require time until they can be verified as effective, and applicable at a larger scale. This is especially true when the mechanism of nitrosamine formation is product-specific.

In cases where the levels of nitrosamines exceed acceptable limits in medicines, such products should in general not be permitted on the market. However, when considering this action, regulators must also balance the impact on the patient if the product is no longer available. This involves determining the availability of alternative treatments and the clinical impact of stopping or switching to a different treatment. In this scenario, regulators need to carefully assess the benefit/risk balance for the specific product. When the risk of not taking the treatment outweighs the risk associated with the nitrosamine impurity, regulators can accept higher interim limits for the impurity on a temporary basis, while the mitigation measures are put in place. This also requires an in-depth quality assessment and a transparent dialogue between the regulator and the manufacturer, so that the interim limit set is as low as possible, and that correct mitigation measures occur promptly.

What is WHO Prequalification Unit - Medicines Assessment Team (PQT/MED) doing regarding nitrosamine impurities?

PQT/MED called for a review on nitrosamines for all API and medicines applications in all therapeutic areas in April 2020. Companies should undertake a risk evaluation by the end of 2020.

Please refer to: <https://extranet.who.int/pqweb/news/manufacturers-conduct-risk-assessments>

For all new products this information will be reviewed before acceptance and prequalification of the product.

Why are there nitrosamine impurities in rifapentine and rifampicin medicines?

1-cyclopentyl-4-nitrosopiperazine (CPNP) and 1-methyl-4-nitrosopiperazine (MeNP) are the specific nitrosamine impurities that have been identified in rifapentine and rifampicin products, respectively. Based on the structure of the impurities and the key manufacturing steps employed by manufacturers, these impurities are expected to be present at varying levels in all rifapentine or rifampicin products. Mitigation measures are needed to reduce their level. These could involve additional purification steps, for example.

Is PQT/MED conducting a risk analysis for nitrosamines in rifapentine and rifampicin?

An initial benefit/risk assessment was conducted as soon as PQT/MED became aware of the presence of nitrosamine impurities in rifapentine and rifampicin products. The consensus has been that the risk to the patient associated with interruption of treatment due to product recalls or suspension of distribution far outweighs any potential future cancer risk associated with the nitrosamine impurity present in the products.

Currently, PQT/MED is conducting product specific risk analysis based on actual reported levels, taking into consideration clinical, toxicological and quality aspects of these medicines. PQT/MED is also in contact with other international regulatory agencies and professional and patient advocacy organizations regarding this issue.

What is PQT/MED specifically doing in relation to CPNP impurity in rifapentine?

Regarding TB336 (Priftin from Sanofi) please refer to our previous note:

<https://extranet.who.int/pqweb/news/nitrosamine-concerns-priftin-rifapentine-update>

Sanofi has informed PQT/MED that TB336 batch 9J2501 distributed to Malawi and Zimbabwe will be replaced by new batches, as requested by the Global Fund. The new batches released by Sanofi meet the CPNP temporary limit of 20 ppm as accepted by USFDA and recognized by PQT/MED. PQT/MED acknowledges that some of the previously distributed TB336 batches might contain slightly higher levels of CPNP impurity, but that this is still acceptable from the point of view of a benefit/risk assessment.

What is PQT/MED specifically doing regarding MeNP impurity in rifampicin?

PQT/MED requested all rifampicin API and medicines applicants to undertake a risk evaluation for nitrosamine impurities by end of 2020. Some of the risk assessment reports have already been submitted and PQT/MED has reviewed them. For these products, the work on mitigation measures by manufacturers has started.

PQT/MED also requested in September 2020 that all rifampicin API and medicines applicants test the MeNP impurity in a representative number of batches. Please refer to:

<https://extranet.who.int/pqweb/news/nitrosamine-concerns-rifapentine-and-rifampicin>

PQT/MED expects to have all rifampicin results in the first quarter of 2021, including risk assessment reports. The required testing of MeNP in rifampicin APIs and medicines will take time, because the analytical procedure must be appropriately validated and shown to be sufficiently sensitive to detect trace levels of this impurity.

For the few APIs for which manufacturers have already reported results, an interim limit is being defined temporarily for the impurity. PQT/MED is closely working with these companies to follow up on mitigation measures that should be applied as soon as possible, in order to decrease the impurity to lifetime acceptable levels.

Given the outcome of the initial risk assessment stated above and results reported so far, PQT/MED has not suspended any of the rifampicin prequalified APIs or medicines. No alert has been considered needed for the time being, and the PQT/MED's recommendation not to interrupt any rifampicin treatment remains.

PQT/MED is closely monitoring the responses related to rifampicin products and the ongoing work by manufacturers.