

Quality Assurance (QA) for Health Products
QA Information Notice

IN N° 2020-08 Version: 24/09/2020	TGF Position on the US FDA approach to mitigate shortages of rifapentine after manufacturer found nitrosamine impurities in his product.
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Addressees

- Any person having products in stock, in transit or under custom clearance through PRs
- Any procurers, buyers with a pending order
- All PRs/ For Information Only
- National Regulatory Authorities and/or Pharmacovigilance Centers through PRs/ For Information Only

Purpose

The Global Fund Quality Assurance Team is issuing this Information Notice to forward information regarding a statement published on the 26th August 2020 by the US FDA in regard of their approach to mitigate shortages of rifapentine after manufacturer found nitrosamine impurities in his product.

Identification of the product(s) and manufacturer

Name of Manufacturer/Manufacturing Site	Sanofi S.p. A, Via Valcanello 4, 03012 Anagni, Italy
INN Name	Rifapentine
Commercial Name(s)	Priftin® 150mg film-coated tablet
Pharmaceutical form	Film-coated tablet
Strength	150 mg
Packaging & Pack size	Blister strip, Alu/Alu 8x3
Batch(es)	Any batches currently on hold/quarantined procured and any batch part of an upcoming procurement for TGF supported programs
Expiry Date	multiple

Background

FDA recently became aware of nitrosamine impurities in certain samples of rifapentine an antibacterial drug used to treat tuberculosis.

CPNP belong to the nitrosamine class of compounds, some of which are classified as probable or possible human carcinogens (substances that could cause cancer), based on laboratory tests such as rodent carcinogenicity studies.

Although there are no data available to directly evaluate the carcinogenic potential of CPNP, information available on closely related nitrosamine compounds was used to calculate lifetime exposure limits for CPNP. The acceptable intake limit is 0.1 ppm for CPNP in rifapentine.

To mitigate or avoid shortages and to help ensure patients have access to these necessary medicines, FDA will not object to certain manufacturers temporarily distributing rifapentine containing 1-cyclopentyl-4-nitrosopiperazine (CPNP)

- above the acceptable intake limits until they can reduce or eliminate the impurities.
- below 14 ppm.

Nature of defect(s)

Details of defect or problem.	OOS in the related Substances
Is there any evidence or suspicion of a risk to public health?	Investigation is on-going at manufacturer's end
Extent of the problem (eg. how many batches).	While waiting for outcomes of the investigation, the present notice is extended to all Batches of Rifapentine manufactured by Sanofi, Anagni that are part of current and upcoming procurement for TGF supported programs
Extent of distribution of the product / batch (es). (based on PQR data)	worldwide
Number of patients potentially impacted	n/a

Action/Investigations taken

- GF raised the issue with WHO PQ
- WHO PQ initiated a risk assessment on the matter.
- GF liaise with GDF on current procurement risks and in particular to identify products critical to patient safety

Next Steps

Based on the information available to date and until further notice, TGF QA team advise to maintain the procurement of the Rifapentine manufactured at Sanofi, Anagni site and procured for Global Fund supported programs under the condition that following requirement is met:

Each batch currently quarantined or “on hold” for distribution, that has been procured for TGF supported programs can be released if the Manufacturer Sanofi, Anagni can demonstrate by performing additional testing activities on each concerned batch, that the level of 1-cyclopentyl-4-nitrosopiperazine (CPNP) content is below 14 ppm.

The same is valid for any upcoming procurement for TGF supported programs until further notice.

TGQ QA Team has taken his decision considering the approach chosen by the US FDA on the temporary tolerated limit of cyclopentyl-4-nitrosopiperazine (CPNP) set to 14 ppm and on the level of assurance provided so far by the ongoing investigation performed by the manufacturer.

TGF QA Team will continue to engage with WHO PQ to follow-up on their approach in regard of this issue.

GF Contacts and acknowledgement

This Information Notice is for information purposes only and does not require a specific written response from the PR.

Please direct any questions about this matter to the technical contacts listed below.

Organisation	Name / Function	E-mail address
Global Fund	Amelie Darmon, Ass. QA Specialist	Amelie.Darmon@theglobalfund.org
Global Drug Facility	Nigorsulton Muzafarova, Lead Product Quality Officer	nigorsultonm@stoptb.org

References:

1. <https://www.fda.gov/drugs/drug-safety-and-availability/fda-works-mitigate-shortages-rifampin-and-rifapentine-after-manufacturers-find-nitrosamine>
2. https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-questions-answers-marketing-authorisation-holders/applicants-chmp-opinion-article-53-regulation-ec-no-726/2004-referral-nitrosamine-impurities-human-medicinal-products_en.pdfAnnex_3- Guidelines on good manufacturing practices: validation, Appendix 7: non-sterile process validation
3. <https://extranet.who.int/prequal/news/manufacturers-conduct-risk-assessments-impurities>