FDA Updates and Press Announcements on Nitrosamine in Varenicline (Chantix)

9/17/2021: UPDATE - Pfizer again expands voluntary Chantix recall

Update [9/17/2021] FDA is alerting patients and health care professionals that Pfizer is expanding its voluntary recall (/safety/recalls-market-withdrawals-safety-alerts/pfizer-expands-voluntary-nationwide-recall-include-all-lots-chantixr-varenicline-tablets-due-n) to include all lots of varenicline (Chantix) 0.5 mg and 1 mg tablets. Pfizer is recalling these lots due to the presence of unacceptable N-nitroso-varenicline levels.

To lessen the impact to patients from a drug shortage due to this ongoing recall, FDA will not object to certain manufacturers distributing varenicline tablets containing N-nitroso-varenicline above FDA's acceptable intake limit of 37 ng per day but below the interim acceptable intake limit of 185 ng per day until the impurity can be eliminated or reduced to acceptable levels.

The agency has temporarily exercised regulatory flexibility and discretion with respect to Apotex's distribution of Health Canada-approved Apo-Varenicline tablets in the U.S. containing N-nitroso-varenicline up to FDA's interim acceptable intake limit in order to help maintain adequate varenicline supply in the U.S. for the near term.

FDA reminds patients taking recalled varenicline to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different treatment. The health benefits of stopping smoking outweigh the cancer risk from the nitrosamine impurity in varenicline.

8/23/2021: Laboratory testing results for nitrosamines in varenicline products

Go to Laboratory Tests | Varenicline (/drugs/drug-safety-and-availability/laboratory-analysis-varenicline-products)

8/18/2021: Pfizer voluntarily recalls additional lots of varenicline (Chantix)

Update [8/18/2021] Pfizer expanded its voluntary recall (/safety/recalls-market-withdrawals-safety-alerts/pfizer-expands-voluntary-nationwide-recall-include-four-additional-lots-chantixr-varenicline-tablets) of varenicline (Chantix) to include 4 additional lots (16 total) to the consumer level. Pfizer is recalling these lots due to the presence of N-nitroso-varenicline above the company's acceptable limit for this impurity.

FDA reminds patients taking recalled varenicline to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition. The health benefits of stopping smoking outweigh the cancer risk from the nitrosamine impurity in varenicline.

7/19/2021: UPDATE - Pfizer expands its voluntary recall of Chantix

Update [7/19/2021] Pfizer expanded its voluntary recall (https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/pfizer-issues-voluntary-nationwide-recall-twelve-lots-chantixr-varenicline-tablets-due-n-nitroso) of varenicline (Chantix) to 12 lots to the consumer level. Pfizer is recalling these lots due to the presence of N-nitroso-varenicline above the company's acceptable limit for this impurity.

Pfizer's recalled lots to date:

Lot number	Expiration date
00020231	9/2021
00020232	11/2021
00020357	12/2021
00020358	1/2022
00020716	1/2022
00019213	1/2022
ET1607	1/2023
ET1609	1/2023
EC6994	5/2023
**ET1600*	*1/2023*
**EA6080*	*3/2023*
**EC9843*	*3/2023*

**most recent additions*

FDA reminds patients taking recalled varenicline to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition. The health benefits of stopping smoking outweigh the cancer risk from the nitrosamine impurity in varenicline.

7/16/2021: UPDATE - FDA not objecting to distribution of varenicline with nitrosamine below interim acceptable intake limit

Update [7/16/2021] To ensure patient access to varenicline, FDA will not object to certain manufacturers temporarily distributing varenicline tablets containing N-nitroso-varenicline above FDA's acceptable intake limit of 37 ng per day but below the interim acceptable intake limit of 185 ng per day until the impurity can be eliminated or reduced to acceptable levels. The agency continues to evaluate data and may update the interim acceptable limit in the future.

Apotex distributes varenicline in Canada under the name Apo-Varenicline. FDA's temporary exercise of regulatory flexibility and discretion with respect to Apotex's distribution of Apo-Varenicline tablets in the U.S. containing N-nitroso-varenicline up to FDA's interim acceptable intake limit of 185 ng per day will help maintain adequate varenicline supply in the U.S. for the near term. See FDA's Drug Shortages (https://www.accessdata.fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm?AI=Varenicline%20Tartrate%20(Chantix)%20Tablets&st=c) page for more information.

Agency scientists evaluated the risk of exposure to N-nitroso-varenicline at interim acceptable intake levels up to 185 ng per day and determined that it presents minimal additional cancer risk when compared to a lifetime of exposure to N-nitroso-varenicline at the 37 ng per day level.

FDA reminds patients taking recalled varenicline to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition. The health benefits of stopping smoking outweigh the cancer risk from the nitrosamine impurity in varenicline.

FDA alerts health care professionals and patients to a voluntary recall of varenicline (Chantix) to the warehouse level

[**7/02/2021**] FDA is alerting patients and health care professionals to Pfizer's voluntary recall of nine lots of the smoking cessation drug, varenicline (brand name Chantix), to the warehouse level. The company is recalling varenicline because it may contain levels of a nitrosamine impurity, called N-nitroso-varenicline, above FDA's acceptable intake limit. N-nitroso-varenicline may be associated with a potential increased cancer risk in humans, but there is no immediate risk to patients taking this medication. An increased cancer risk would be associated with long-term use, and the health benefits of stopping smoking outweigh the cancer risk from the nitrosamine impurity in varenicline.

Recalled lots:

Lot number	Expiration date
00020231	9/30/2021
00020232	11/30/2021
00020357	12/31/2021
00020358	1/31/2022
00020716	1/31/2022
00019213	1/31/2022
ET1607	1/31/2023
ET1609	1/31/2023
EC6994	5/31/2023

N-Nitroso-varenicline belongs 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 N-nitroso-varenicline, information available on closely related nitrosamine compounds was used to calculate lifetime exposure limits for N-nitroso-varenicline.

Pfizer is recalling the varenicline lots currently stored in warehouses. FDA recommended Pfizer revise its recall to the consumer level in order to take into account the product currently on the market, but the company has not yet done so.

In addition to the voluntary recall, Pfizer is holding release of varenicline to the U.S. market until it can confirm N-nitroso-varenicline levels below what the company considers to be acceptable.

What patients should know:

- Continue taking your current medicine until your doctor or pharmacist gives you a replacement or a different treatment option.
- Contact your health care professional if you are taking this medication and have questions about your health.

What health care professionals should know:

- FDA has determined the recalled varenicline poses an unnecessary risk to patients. Therefore, FDA recommends health care professionals consider other available treatment options for the patient's medical condition.
- If you have varenicline samples from this company, quarantine them, and do not provide them to patients.
- Contact Pfizer directly if you have questions regarding product return or disposal.

FDA is actively considering options to help mitigate a shortage of varenicline in the U.S. including working to identify an alternate supplier. The agency is continuing to investigate the presence of N-nitroso-varenicline in varenicline products and will provide more information as it becomes available.

We know impurities in medicines are of great concern to patients and consumers who rely on safe and effective medicines approved by FDA, and we are working with manufacturers and global regulators to provide clear and actionable information. In September 2020, FDA published a guidance for industry entitled "*Control of N-Nitrosamine Impurities in Human Drugs* (/media/141720/download)." This guidance recommends steps manufacturers of active pharmaceutical ingredients (APIs) and drug products should take to detect and prevent objectionable levels of nitrosamine impurities in pharmaceutical products.

Today, we have better testing methods than ever before, and we have a better understanding of what to look for in products' chemical structure and manufacturing processes that may increase the risk of forming low levels of impurities. Improved technology enables us to detect even trace amounts of impurities in drug products and may be the reason why more products have been recently found to have detectable levels of nitrosamines.

FDA continues its ongoing review, surveillance, compliance and pharmaceutical quality efforts across every product area and will continue to work with drug manufacturers to ensure safe, effective and high-quality drugs for the American public.

Patients and health care professionals should report any adverse reactions with varenicline to FDA's MedWatch program (/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program) to help the agency better understand the scope of the problem:

- Complete and submit the report online at www.fda.gov/medwatch/report.htm (https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home)
- Download and complete the appropriate form (/safety/medical-product-safety-information/medwatch-forms-fda-safety-reporting), then submit it via fax at 1-800-FDA-0178

FDA-published testing method to provide an option for regulators and industry to detect nitrosamine impurities

The link below is to an FDA-published testing method to provide an option for regulators and industry to detect nitrosamine impurities in varenicline drug substances and drug products. This method should be validated by the user if the resulting data are used to support a required quality assessment of the API or drug product, or if the results are used in a regulatory submission.

- LC-ESI-HRMS method (/media/151470/download): A reverse phase LC method with HRMS detection for the determination of varenicline NDSRI in Chantix™ drug product or drug substance.