



2021 Varenicline Update Regarding Nitrosamine Contaminants

Douglas Jorenby, PhD and Michael Fiore, MD, MPH, MBA
University of Wisconsin Center for Tobacco Research and Intervention
September 15, 2021

What we know:

- As a result of ongoing FDA concerns dating back to at least 2019 regarding nitrosamine impurities in medications (metformin, ranitidine, etc.), the FDA in September 2020 established an acceptable intake limit (AI) of varenicline nitrosamine impurities at 37 nanograms/18.5 ppm. This limit was based upon an estimated increased risk of cancer of in one individual among 100,000 taking a drug containing that nitrosamine every day for 70 years at that AI or greater.
- Pfizer identified N-nitroso-varenicline (a novel nitrosamine) in samples of varenicline produced by them in the summer of 2021 (see also 24 Feb 2021 FDA *Guidance to Industry*). Some tested lots of varenicline contained 150-470 ng per tablet (155-474 ppm).
- On 16 July 2021, Pfizer voluntarily recalled 10 lots of 0.5 and 1 mg varenicline tablets. These had been distributed to nationwide wholesalers and distributors between June 2019 and June 2021.
- On 16 July 2021, the FDA allowed a Canadian-approved drug product, Apo-Varenicline (in 0.5 and 1 mg tablets) to be distributed in the US. Testing of Apo-Varenicline revealed per tablet levels of N-nitroso-varenicline of 14-44 ng (27-44 ppm).
- On 11 Aug 2021, the FDA approved a varenicline product produced by Par Pharmaceuticals that contained N-nitroso-varenicline at levels of 3 ng/per 1 mg tablet (3 ppm).
- On 16 Aug 2021, Pfizer voluntarily recalled an additional four lots of 0.5 and 1 mg varenicline tablets based upon additional testing results.

What we do not know

- Pfizer has argued that given the episodic use indication for varenicline (e.g., 12 week treatment regimen) an AI standard of 70 years of daily use is not an appropriate risk standard given most individuals take varenicline for 3-6 months. This argument has been advanced with both the US FDA and the European Medicines Agency, but has not yet resulted in a change of the AI standard.
- Testing of varenicline for levels of N-nitroso-varenicline is ongoing. It is possible that additional lots exceeding the current AI may be identified.
- Because N-nitroso-varenicline is a novel nitrosamine, it is unclear what, if any, long-term risk it may pose to users.
- As with other medications found to contain nitrosamine impurities, it is unclear whether the impurities are a result of storage, packaging, manufacturing processes, or the chemical structure of specific medications.
- It is unclear whether the FDA temporary exercise of regulatory flexibility and discretion regarding use of Apo-varenicline extends to its use in research studies.
- It is unclear whether the FDA temporary exercise of regulatory flexibility and discretion regarding use of Apo-varenicline only applies to persons currently taking varenicline or whether FDA advice regarding use of alternatives to varenicline still applies to persons not using varenicline.
- It is unclear whether the FDA plans to issue any additional guidance to patients, healthcare providers, and IRBs regarding use of non-Pfizer varenicline products.
- No guidance has been provided by the FDA or the NIH regarding the research use of varenicline given the nitrosamine impurities.