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Could APO-varenicline and cytisine be solutions for the shortage of varenicline in Brazil?

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The presence of N-nitrosamines in pharmaceutical products gained notoriety in 2018, when the regulatory agencies European Medicine Agency and U.S. Food and Drug Administration (FDA) became aware of the presence of N-nitrosodimethylamine in angiotensin II receptor antagonists (known as belonging to the group of sartans).[1] After that, there has been a concomitant recall of these drugs in the United States, European countries, Australia, and New Zealand.

On June 9, 2021, Pfizer Brazil announced that its varenicline tartrate, marketed in Brazil as Champix®, in all its forms would undergo a temporary withdrawal.[2] No mention to a nitrosamine impurity was made. On July 16, 2021 Pfizer USA issued a voluntary recall for twelve lots of varenicline distributed in the United States and Puerto Rico between June of 2019 and June of 2021 due to the presence of a nitrosamine.[3] Over the next couple of months, both Pfizer USA and Pfizer Europe voluntarily recalled other lots of varenicline, also due to elevated amounts of N-nitroso-varenicline (NNV), and subsequently announced the interruption of production and distribution of the drug globally.[4]

There was a significant reduction of varenicline use by the limited delivery of the drug to pharmacies and its consequent withdrawal from all the world market. According to Lang et al.,[5] during the restriction period in the USA (between January of 2021 and June of 2022), no increase in the prescription/consumption of any form of nicotine replacement therapy (NRT) or prolonged-release bupropion was detected. The authors emphasized that a considerable number of smokers would probably have given up their smoking cessation treatment. That study did not take account of the consumption of the aforementioned drugs without medical prescription (over-the-counter NRT purchases), since the study was limited only to those with commercial insurance.[5]

In August of 2021, the FDA released its laboratory analysis of varenicline products available in the USA, informing NNV levels above FDA's acceptable intake limit in some samples.[6] In the same document, the Agency described the analytical methods to be used in laboratory testing.[6] Few months later, in November of 2021, the FDA published an update on risk mitigation strategies, encouraging manufacturers to explore the approaches to attenuate or prevent the formation of impurities.[7] After the detection of NNV, different approaches to control impurities could have been used. Safety-based limits, such as permissible daily exposure, acceptable intake, threshold of toxicological concern, and less-than-lifetime limits were all possibilities.[8]

FDA scientists stated that NNV might increase the risk of cancer if the exposure is above the acceptable intake limit and over a prolonged period.[6] However, a person taking a drug containing NNV at or below the acceptable intake limit every day for 70 years was not expected to have an increased risk of cancer. The FDA concluded that consuming up to 37 ng of NNV/day, the acceptable intake limit, was reasonably safe for humans.[6] The Agency also evaluated the risk of exposure to NNV at levels up to 185 ng per day and found a minimal additional cancer risk when compared with a lifetime of exposure to NNV.[6]

These movements and findings of international agencies had repercussions in the Brazilian *Agência Nacional de Vigilância Sanitária* (ANVISA, Health Regulatory Agency) and in Pfizer Brazil, the international manufacturer of this medication.

On July 6, 2021, the ANVISA issued Guide 50 version 1 to help "varenicline sponsors" further investigate and handle the issue of varenicline contamination with nitrosamine impurities. Later on, the ANVISA launched a public consultation on this subject to assess the risks of using the drug and how to control the potentially carcinogenic nitrosamines for human use.[9] On May 4, 2022, the ANVISA released the second version of Guide 50/2022[10] and published the Collegiate Directorate Resolution no. 677/2022 on the control of nitrosamines in acceptable intake limits.[11] The new version of the guide entered into force immediately and the Resolution established that pharmaceutical companies should develop a risk matrix clearly defining the sequence of evaluation of the products in their portfolio, contemplating the risk categories as "very high", "high", "medium", "low", and "very low".[11]

Pharmaceutical companies must meet the requirements set forth in that Resolution for risk assessment of products classified as at a "very high" risk by March 1, 2023: that was the deadline for Pfizer Brazil and its varenicline medication. A review on the development of the analytical methods for determining nitrosamine and N-nitroso impurities in pharmaceuticals has been published recently.[12]

The smoking cessation landscape in Brazil has been worrisome for quite a while. Apart from the continued shortage of varenicline since 2020,[13] there has been a scarcity of NRT in all its forms in several health care facilities of the Brazilian *Sistema Público de Saúde* (SUS, Unified Health Care System). Unfortunately, there are no resupply dates yet. As far as we know, the Brazilian Ministry of Health has not yet considered importing APO-varenicline, the generic varenicline tartrate product

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approved by international agencies as a generic equivalent to Champix® tablets.

An alternative to Pfizer's varenicline is the generic varenicline tartrate tablets produced by PAR Pharmaceutical (Woodcliff Lake, NJ, USA), which has already been approved by the FDA.[6] In addition there is also APO-varenicline® tablets (Apotex Corp, Toronto, Canada), which is available in North America and Australia. Both generic products contain levels of NNV impurity below the acceptable intake and could/should be imported to enable Brazilian smokers to be motivated to quit their drug addiction more easily.

Another possibility could be cytisine, an alkaloid that binds with high affinity to nicotinic acetylcholine alpha4-beta2 receptors, the very same mechanism of action of varenicline. Cytisine has been used in several countries in Eastern Europe since the 1960s as a low-cost alternative in smoking cessation. It is now available over the counter as a useful drug for smoking cessation in 18 European countries, including Italy, Poland, and Portugal.[14]

In 2014, Walker et al.[15] reported that, when combined with brief behavioral support, cytisine was superior to NRT in helping smokers quit smoking, but it was associated with a higher frequency of self-reported adverse events. The most common adverse events were gastrointestinal symptoms, comprising abdominal swelling, gastritis, and constipation. More recently, Walker et al.[14] conducted another study to determine whether cytisine was at least as effective as varenicline in supporting smoking abstinence for ≥ 6 months in New Zealand indigenous populations. Smokers received a prescription for 12 weeks of cytisine or varenicline, plus low-intensity cessation behavioral support from the prescribing doctor and community stop-smoking services or a research assistant. Continuous abstinence rates at 6 months post-cessation date were 12.1% in cytisine users vs. 7.9% in varenicline users (risk difference, 4.29%; relative risk = 1.55).[15] At the 12-month follow-up in the latter study, the smoking cessation rate was 32.1% in the intervention arm and 7.3% in the control arm).[14] The adjusted OR for continuous abstinence was 7.2 (95% CI, 4.6-11.2).[14] Self-reported adverse events over 6 months significantly occurred more frequently in the varenicline group (varenicline: 509 events in 138 participants vs. cytisine: 313 events in 111 participants), with incidence rate ratio of 0.56. Common adverse events were nausea, headache, and difficulty in sleeping. The authors concluded that cytisine, a very low-cost medication, is safe and at least as effective as varenicline in supporting smoking cessation.[14]

Courtney et al.[16] failed to demonstrate noninferiority of cytisine compared with varenicline regarding smoking cessation. It should be considered, however, that the authors adopted the standard 25-day treatment regimen for cytisine, which sets the cessation date at day 5 after initiation of the medication. At the end of the first month (at which point the cytisine treatment was finished), self-reported abstinence in the previous week were 42.5% and 32.3% with the use of cytisine and varenicline, respectively.[16] Another important point regarding that clinical trial was that the behavioral support was close to none: participants got only a referral to a telephone smoking cessation line.[16] Thus, it would be worth testing a longer treatment period with cytisine with appropriate behavioral support in future studies.

There has been some private research investment on cytisine following the commercialization and patent of cytisine succinate[16] and mesylate salts[17] as new drug products. A simplified dosing cytisine regimen (1.5 mg and 3 mg three times daily) with two administration schedules (commercial titration vs. simplified three times daily) within a 25-day treatment period was tested in the a multicenter, double-blind, randomized, placebo-controlled phase 2b trial conducted in the USA.[18] Patients received 12 behavioral support sessions by a qualified staff member plus supportive literature and online resources. The 3-mg dose/schedule three times a day (no titration)[18] was selected for further evaluation in a phase 3 program that was designed to evaluate the efficacy and safety of 3-mg dose three times daily when compared with placebo and also longer treatment schedules (like Courtney et al.[16] suggested) to reduce potential relapses in smoking. Both studies have been completed; the second study completion date was March 21, 2023.[19] Their results have not been published yet. Achieve Life Sciences intends to develop and commercialize cytisine (also known as cytisinicline) in the USA, and thereafter to target other markets such as Western Europe, Japan, and Latin America.[20]

There have been some interactions between regulators and industry to address how NNV should be controlled, but the FDA has not changed its 2020 update guidance yet. A "nitrites in excipients" database has been developed by the industry to facilitate risk assessment of drug products,[21,22] but there are still gaps in knowledge on novel nitrosamines and more research is needed to address nitrosamine impurities. Getting rid of NNV is a Herculean task: a number of factors are involved, including the chemical structure of varenicline, manufacturing processes, storage, and/or packaging conditions.

Pfizer's varenicline, the most effective smoking cessation drug, has been unavailable in Brazil since 2020 and will not be available in the near future (if it will ever be again). However, there are generic varenicline tartrate products in the global market that are available for quite some time in many countries. Law no. 12,401 created the Brazilian National Committee for Technology Incorporation, defining both the criteria and deadlines for technology incorporation in the SUS.[23] The committee is responsible for advising the Brazilian Ministry of Health regarding the incorporation or disinvestment of health technologies in the SUS and development of clinical guidelines.[23] The time has come for the Committee to start the process of incorporation of APO-varenicline within the SUS.

AUTHOR CONTRIBUTIONS

The authors equally contributed to this work.

CONFLICTS OF INTEREST

None declared.

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