4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2022-P-1013]

Determination That CHANTIX (Varenicline Tartrate) Tablets, 0.5 Milligram and 1 Milligram, Has not Been Withdrawn from Sale for Reasons of Safety or Effectiveness

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA or Agency) has determined that CHANTIX (varenicline tartrate) tablets, 0.5 milligram (mg) and 1 mg, has not been withdrawn from sale for reasons of safety or effectiveness to the extent that the drug can be manufactured or formulated in a manner that satisfies any applicable acceptable intake limit for nitrosamine impurities. This determination means that FDA will not begin procedures to withdraw approval of abbreviated new drug applications (ANDAs) that refer to this drug product, and it will allow FDA to continue to approve ANDAs that refer to the product as long as they meet relevant legal and regulatory requirements.

FOR FURTHER INFORMATION CONTACT: David Faranda, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6258, Silver Spring, MD 20993-0002, 301-796-8767, David.Faranda@fda.hhs.gov.

SUPPLEMENTARY INFORMATION: Section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)) allows the submission of an ANDA to market a generic version of a previously approved drug product. To obtain approval, the ANDA applicant must show, among other things, that the generic drug product: (1) has the same active ingredient(s), dosage form, route of administration, strength, conditions of use, and (with certain exceptions) labeling as the listed drug, which is a version of the drug that was previously

approved, and (2) is bioequivalent to the listed drug. ANDA applicants do not have to repeat the extensive clinical testing otherwise necessary to gain approval of a new drug application (NDA).

Section 505(j)(7) of the FD&C Act requires FDA to publish a list of all approved drugs. FDA publishes this list as part of the "Approved Drug Products With Therapeutic Equivalence Evaluations," which is known generally as the "Orange Book." Under FDA regulations, drugs are removed from the list if the Agency withdraws or suspends approval of the drug's NDA or ANDA for reasons of safety or effectiveness or if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (21 CFR 314.162).

A person may petition the Agency to determine, or the Agency may determine on its own initiative, whether a listed drug has been withdrawn from sale for reasons of safety or effectiveness. This determination may be made at any time after the drug has been withdrawn from sale, but must be made prior to approval of an ANDA that refers to the listed drug (§ 314.161 (21 CFR 314.161)). FDA may not approve an ANDA that does not refer to a listed drug.

CHANTIX (varenicline tartrate) tablets, 0.5 mg and 1 mg, is the subject of NDA 021928, held by PF Prism CV (c/o Pfizer Inc.), and initially approved on May 10, 2006. CHANTIX is indicated for use as an aid to smoking cessation treatment.

PF Prism CV has voluntarily discontinued marketing of CHANTIX (varenicline tartrate) tablets, 0.5 mg and 1 mg. The levels of the N-nitroso-varenicline (NNV) impurity in Chantix exceeded FDA's acceptable intake limit.[1] FDA's current understanding is that the NNV

[1] Nitrosamine impurities in the drug supply are an important public health concern to which the Agency is dedicating significant resources. As explained in FDA's Guidance for Industry, *Control of Nitrosamine Impurities in Human Drugs*, "Nitrosamine compounds are potent genotoxic agents in several animal species and some are classified as probable or possible human carcinogens by the International Agency for Research on Cancer (IARC). They are referred to as "cohort of concern" compounds in the ICH guidance for industry *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk* (March 2018)." Many drug products have been found to contain levels of nitrosamines that are unacceptable or require further evaluation. FDA's current understanding is that nitrosamine levels in affected drug products have different causes and may be controlled using different strategies, including formulation design (i.e., adding antioxidants or adding pH adjusters that modify the microenvironment to base or neutral pH) and supplier qualification programs.

impurity can be controlled within the acceptable intake limit by sponsors of varenicline products within the context of their particular applications.

CHANTIX (varenicline tartrate) tablets, 0.5 mg and 1 mg, is currently listed in the "Discontinued Drug Product List" section of the Orange Book.

Medley Pharmaceuticals Ltd. submitted a citizen petition dated June 6, 2022 (Docket No. FDA-2022-P-1013), under 21 CFR 10.30, requesting that the Agency determine whether CHANTIX (varenicline tartrate) tablets, 0.5 mg and 1 mg, were withdrawn from sale for reasons of safety or effectiveness.

After considering the citizen petition and reviewing Agency records and based on the information we have at this time, FDA has determined under § 314.161 that CHANTIX (varenicline tartrate) tablets, 0.5 mg and 1 mg, has not been withdrawn for reasons of safety or effectiveness to the extent that the drug can be manufactured or formulated in a manner that satisfies any applicable acceptable intake limit for nitrosamine impurities.

Accordingly, the Agency will continue to list CHANTIX (varenicline tartrate) tablets, 0.5 mg and 1 mg, in the "Discontinued Drug Product List" section of the Orange Book. The "Discontinued Drug Product List" delineates, among other items, drug products that have been discontinued from marketing for reasons other than safety or effectiveness. FDA will not begin procedures to withdraw approval of approved ANDAs that refer to this drug product. Additional ANDAs for this drug product may be approved by the Agency as long as they meet all other legal and regulatory requirements for the approval of ANDAs, including satisfying any applicable acceptable intake limit for nitrosamine impurities. If FDA determines that labeling for this drug product should be revised to meet current standards, the Agency will advise ANDA applicants to submit such labeling.

Dated: February 22, 2023.

Lauren K. Roth,

Associate Commissioner for Policy.

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