4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2024-P-5470]

Determination That RIFADIN (Rifampin) Capsules, 150 Milligrams and 300 Milligrams, Were Not Withdrawn from Sale for Reasons of Safety or Effectiveness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(FDA or Agency) has determined that RIFADIN (rifampin) capsules, 150 milligrams (mg) and 300 mg, were not withdrawn from sale for reasons of safety or effectiveness to the extent that the drugs can be manufactured or formulated in a manner that satisfies any applicable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 these drug products, and it will allow FDA to continue to approve ANDAs that refer to the products as long as they meet relevant legal and regulatory requirements, including satisfying any applicable acceptable intake limit for nitrosamine impurities.

FOR FURTHER INFORMATION CONTACT: Robin Fastenau, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6236, Silver Spring, MD 20993-0002, 240-893-4962, robin.fastenau@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 was 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 it 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.

RIFADIN (rifampin) capsules, 150 mg and 300 mg, are the subject of NDA 050420, held by Sanofi Aventis US LLC, and initially approved on May 21, 1971. RIFADIN (rifampin) capsules, 150 mg and 300 mg, are indicated for the treatment of all forms of tuberculosis and for the treatment of asymptomatic carriers of *Neisseria meningitidis* to eliminate meningococci from the nasopharynx.

RIFADIN (rifampin) capsules, 150 mg and 300 mg, have not been marketed in the United States since their voluntary discontinuation from sale in November 2020.

Novitium Pharma LLC submitted a citizen petition dated November 21, 2024 (Docket No. FDA-2024-P-5470), under 21 CFR 10.30, requesting that the Agency determine whether RIFADIN (rifampin) capsules, 150 mg and 300 mg, were withdrawn from sale for reasons of safety or effectiveness.

FDA has identified a number of active pharmaceutical ingredients (APIs) that have secondary or tertiary amines and are therefore at risk for forming nitrosamine drug substance

related impurities (NDSRIs). Hypothetically, under certain conditions related to the formulation and manufacturing process for the drug product, such as residual nitrites in excipients used to formulate the drug product, these APIs could form NDSRIs. Rifampin is one such API at risk of forming 1-methyl-4-nitrosopiperazine (MNP). FDA has tested certain rifampin products for MNP and detected MNP in all such tested rifampin products.[1] FDA has announced recommended acceptable intake limits for MNP in all rifampin products, including a recommended interim acceptable intake limit. Rifadin (rifampin) 150 mg and 300 mg capsules are currently listed in the "Discontinued Drug Product List" section of the Orange Book.

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 RIFADIN (rifampin) capsules, 150 mg and 300 mg, were not withdrawn for reasons of safety or effectiveness to the extent that the drugs can be manufactured or formulated in a manner that satisfies any applicable acceptable intake limit for nitrosamine impurities. The petitioner has identified no data or other information suggesting that RIFADIN (rifampin) capsules, 150 mg and 300 mg, were withdrawn for reasons of safety or effectiveness. We have carefully reviewed our files for records concerning the withdrawal of RIFADIN (rifampin) capsules, 150 mg and 300 mg, from sale. We have also independently evaluated relevant literature and data for possible postmarketing adverse events. We have reviewed the available evidence and determined that these drug products were not withdrawn from sale for reasons of safety or effectiveness to the extent that the drugs can be

[1] Nitrosamine impurities in the drug supply are an important public health concern. As explained in the guidance for industry entitled "Control of Nitrosamine Impurities in Human Drugs" published September 2024 (available at https://www.fda.gov/media/141720/download) (at 4–5), "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. They are referred to as *cohort of concern* compounds in the International Council for Harmonisation of Technical Requirements for . . . Human Use (ICH) guidance for industry *M7(R2) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* (July 2023)." 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.

manufactured or formulated in a manner that satisfies any applicable acceptable intake limit for nitrosamine impurities.

Accordingly, the Agency will continue to list RIFADIN (rifampin) capsules, 150 mg and 300 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 these drug products. Additional ANDAs for these drug products may also 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 these drug products should be revised to meet current standards, the Agency will advise ANDA applicants to submit such labeling.

Dated: August 14, 2025.

Grace R. Graham,

Deputy Commissioner for Policy, Legislation, and International Affairs.

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