4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2023-P-2874]

Determination That Romidepsin Injection, 10 Milligrams/2 Milliliters (5 Milligrams/Milliliter) and 27.5 Milligrams/5.5 Milliliters (5 Milligrams/Milliliter), Were Not Withdrawn From Sale for Reasons of Safety or Effectiveness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that Romidepsin Injection, 10 milligrams (mg)/2 milliliters (mL) (5 mg/mL) and 27.5 mg/5.5 mL (5 mg/mL), were not withdrawn from sale for reasons of safety or effectiveness. This determination will allow FDA to approve abbreviated new drug applications (ANDAs) for romidepsin solution, 10 mg/2 mL (5 mg/mL) and 27.5 mg/5.5 mL (5 mg/mL), that refer to these drugs as long as they meet relevant legal and regulatory requirements.

FOR FURTHER INFORMATION CONTACT: Veniqua Stewart, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6219, Silver Spring, MD 20993-0002, 301-796-3267, Veniqua.Stewart@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approval of the drug's NDA or ANDA for reasons of safety or effectiveness or if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (21 CFR 314.162).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 must be made prior to approving 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.

Romidepsin Injection, 10 mg/2 mL (5 mg/mL) and 27.5 mg/5.5 mL (5 mg/mL), are the subject of NDA 208574, held by Teva Pharmaceuticals USA, Inc. (Teva), and initially approved on March 13, 2020. Romidepsin Injection is currently indicated only for the treatment of cutaneous T-cell lymphoma (CTCL) in adult patients who have received at least one prior systemic therapy.

Romidepsin Injection, 10 mg/2 mL (5 mg/mL) and 27.5 mg/5.5 mL (5 mg/mL), are currently listed in the "Discontinued Drug Product List" section of the Orange Book.

E. Rust Consulting, LLC submitted a citizen petition dated July 11, 2023 (Docket No. FDA-2023-P-2874), under 21 CFR 10.30, requesting that the Agency determine whether Romidepsin Injection, 10 mg/2 mL (5 mg/mL) and 27.5 mg/5.5 mL (5 mg/mL), 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 Romidepsin Injection, 10 mg/2 mL (5 mg/mL) and 27.5 mg/5.5 mL (5 mg/mL), were not withdrawn for reasons of safety or effectiveness. The petitioner has identified no data or other information

suggesting that Romidepsin Injection, 10 mg/2 mL (5 mg/mL) and 27.5 mg/5.5 mL (5 mg/mL), were withdrawn for reasons of safety or effectiveness. We have carefully reviewed our files for records concerning the withdrawal of Romidepsin Injection, 10 mg/2 mL (5 mg/mL) and 27.5 mg/5.5 mL (5 mg/mL), from sale. We have also independently evaluated relevant literature and data for possible postmarketing adverse events.

We note that Romidepsin Injection, 10 mg/2 mL (5 mg/mL) and 27.5 mg/5.5 mL (5 mg/mL), previously were approved with an indication for treatment of peripheral T-cell lymphoma (PTCL) in adult patients who have received at least one prior therapy, under the Agency's accelerated approval regulations, 21 CFR part 314, subpart H. The accelerated approval of Teva's Romidepsin Injection for PTCL included a required postmarketing clinical trial intended to verify the clinical benefit of romidepsin (the Ro-CHOP study) for PTCL. Teva's Romidepsin Injection product was approved under the 505(b)(2) approval pathway, and the listed drug relied upon is Celgene Corp.'s (Celgene) NDA 022393, ISTODAX (romidepsin) for injection, 10 mg/vial. Celgene was acquired by Bristol-Meyers Squib Co. which is currently listed as the NDA holder in the Orange Book.

On August 6, 2020, Celgene submitted high level results from the Ro-CHOP study to FDA, which indicated the study failed to meet its primary endpoint of progression-free survival. On May 14, 2021, Celgene informed FDA that after careful consideration, Celgene decided to voluntarily withdraw the PTCL indication from ISTODAX (romidepsin) for injection, 10 mg/vial. On June 17, 2021, Celgene submitted a supplemental NDA proposing to remove the PTCL indication. On July 14, 2021, Celgene submitted a letter asking FDA to withdraw approval of the PTCL indication pursuant to § 314.150(d) (21 CFR 314.150(d)) and waiving its opportunity for a hearing.

On August 27, 2021, Teva submitted a labeling supplement proposing to remove the PTCL indication. On September 12, 2021, the Agency requested Teva voluntarily request withdrawal of the PTCL indication pursuant to § 314.150(d) and waive its opportunity for a

hearing. On September 14, 2021, Teva amended its supplement by submitting a cover letter requesting withdrawal of approval of the PTCL indication pursuant to § 314.150(d) and waiving its opportunity for a hearing. On December 8, 2021, FDA approved the supplemental NDA to revise the labeling to remove the PTCL indication. In the *Federal Register* of May 9, 2022 (87 FR 27644), FDA announced that it was withdrawing approval of the PTCL indications for ISTODAX (romidepsin) for injection, 10 mg/vial, and Romidepsin Injection. Therefore, Romidepsin Injection is only indicated for the treatment of CTCL in adult patients who have received at least one prior systemic therapy.

The Agency will continue to list Teva's Romidepsin Injection, 10 mg/2 mL (5 mg/mL) and 27.5 mg/5.5 mL (5 mg/mL), 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 accept and, where appropriate, approve ANDAs that refer to these drug products, but does not intend to do so if they propose to include the PTCL indication (see, e.g., section 505(j)(2)(A)(v) and (j)(4)(G) of the FD&C Act and 21 CFR 314.94(a)(8)(iv) and 314.127(a)(7)). 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: March 8, 2024.

Lauren K. Roth,

Associate Commissioner for Policy.

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