DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

CERTIFIED MAIL-RETURN RECEIPT REQUESTED

Teva Pharmaceuticals
Attention: Barinder Sandhu
Senior Director, Regulatory Affairs, US Generics
425 Privet Road
Horsham, PA 19044

4/19/2016

Dear Madam:

This letter is being sent under Section 506C(f) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for the reasons set forth below.

Section 506C of the FD&C Act requires a manufacturer of a drug product that is "life-supporting, life-sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition" to notify the Food and Drug Administration (FDA or the Agency) of: (1) a permanent discontinuance in the manufacture of the drug; or (2) an interruption of the manufacture of the drug that is likely to lead to a meaningful disruption[1] in the supply of that drug in the United States; and (3) the reason(s) for such discontinuance or interruption of manufacturing (FD&C Act § 506C(a)). The notification must be submitted at least 6 months prior to the date of the discontinuance or interruption of manufacturing, or as soon as practicable (FD&C Act § 506C(b)). Compliance with this notification requirement is essential to facilitating the mitigation and/or prevention of a shortage or potential shortage, and ultimately may ensure availability of critical drugs for patients.

If a person fails to submit this required notification within the required timeframe, FDA must issue a letter to that person informing the person of the failure to comply with the FD&C Act (FD&C Act § 506C(f)).

Tretinoin capsules are a product that is "life-supporting, life-sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition." This product has an approved indication for the induction of remission in patients with acute promyelocytic leukemia (APL), French-American-British (FAB) classification M3 (including the M3 variant), characterized by the presence of the t(15;17) translocation and/or the presence of the PML/RARα gene who are refractory to, or who have relapsed from, anthracycline chemotherapy, or for whom anthracycline-based chemotherapy is contraindicated. It is our understanding that sometime between January and February 2016, there was an interruption in the manufacture of tretinoin capsules. This interruption was likely to lead to a meaningful disruption in the supply of this drug product in the United States. The Agency learned of the disruption from outside stakeholders in February 2016, and tretinoin capsules were determined to be in shortage soon thereafter, on February 19, 2016. Our records indicate that Teva Pharmaceuticals did not notify FDA of the interruption in manufacture of this product. Accordingly, we are issuing you this letter to notify you of your noncompliance with the FD&C Act.

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1 The statute defines "meaningful disruption" to mean "a change in production that is reasonably likely to lead to a reduction in the supply of a drug by a manufacturer that is more than negligible and affects the ability of the manufacturer to fill orders or meet expected demand for the product," and "does not include interruptions in manufacturing due to matters such as routine maintenance or insignificant changes in manufacturing so long as the manufacturer expects to resume operations in a short period of time." Section 506C(h)(3).

No later than thirty calendar days after the issuance of this letter, you must submit to the Agency a written response setting forth the basis for noncompliance with Section 506C and providing the required notification, including the reason(s) for the interruption in manufacturing that led to a disruption in the supply of tretinoin capsules in February 2016.

No later than forty-five calendar days after the issuance of this letter, FDA will make this letter and your response to the letter available to the public on FDA's Drug Shortage website, unless the Agency determines that this letter was issued in error, or, after review of your response, determines that there was a reasonable basis for noncompliance. In posting the letter and your response on the Drug Shortage website, FDA would protect confidential commercial information and trade secrets, if any, as required by applicable law.

If you have further questions, please contact the Drug Shortage Staff at (301) 796-1300.

Please submit all communications regarding this drug product to the following address:

Drug Shortage Staff
Food and Drug Administration
WO 22, Room 6204
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely,

CAPT Valerie Jensen
Associate Director
Drug Shortage Staff
Center for Drug Evaluation and Research