

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2002P-0399]

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Determination That ESTROSTEP 21 (Ethinyl Estradiol and Norethindrone Acetate) Tablets Were Not Withdrawn From Sale for Reasons of Safety or Effectiveness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Administration (FDA) has determined that ESTROSTEP 21 (ethinyl estradiol and norethindrone acetate) tablets were not withdrawn from sale for reasons of safety or effectiveness. This determination will allow FDA to approve abbreviated new drug applications (ANDAs) for the combination drug ethinyl estradiol and norethindrone acetate tablets, 0.02 milligram (mg)/1 mg, 0.03 mg/1 mg, and 0.035 mg/1 mg.

FOR FURTHER INFORMATION CONTACT: Mary Catchings, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-2041.

SUPPLEMENTARY INFORMATION: In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the 1984 amendments), which authorized the approval of duplicate versions of drug products approved under an ANDA procedure. ANDA sponsors must, with certain exceptions, show that the drug for which they are seeking approval contains the same active ingredient in the same strength and dosage form as the "listed drug," which is typically a version of the drug that was

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previously approved. Sponsors of ANDAs do not have to repeat the extensive clinical testing otherwise necessary to gain approval of a new drug application (NDA). The only clinical data required in an ANDA are data to show that the drug that is the subject of the ANDA is bioequivalent to the listed drug.

The 1984 amendments include what is now section 505(j)(7) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(7)), which 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 generally known 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of the drug's NDA or ANDA for reasons of safety or effectiveness, or if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (§ 314.162)(21 CFR 314.162)).

Under § 314.161(a)(1)(21 CFR 314.161(a)(1)), the agency must determine whether a listed drug was withdrawn from sale for reasons of safety or effectiveness before an ANDA that refers to that listed drug may be approved. FDA may not approve an ANDA that does not refer to a listed drug.

ESTROSTEP 21 (ethinyl estradiol and norethindrone acetate) tablets, 0.02 mg/1 mg, 0.03 mg/1 mg, and 0.035 mg/1 mg, are the subject of approved NDA 20-130 held by Warner Chilcott. ESTROSTEP 21 tablets, 0.02 mg/1 mg, 0.03 mg/1 mg, and 0.035 mg/1 mg, were approved on October 9, 1996, as oral contraceptives indicated for the prevention of pregnancy in women who elect to use these products as a method of contraception. FDA also approved ESTROSTEP FE under NDA 20-130 on October 9, 1996, for the same indication. On July 1, 2001, FDA approved ESTROSTEP 21 and ESTROSTEP FE for the treatment of moderate acne vulgaris under NDA 21-276. Both

ESTROSTEP 21 and ESTROSTEP FE provide a gradually increasing estrogen dose with a constant dose of progestin. Both drugs provide the same dosage regimen of oral contraceptive tablets for the first 21 days of a 28-day cycle. ESTROSTEP FE provides an additional seven ferrous fumarate tablets. The ferrous fumarate tablets, which are nonhormonal and serve no therapeutic purpose, are added to facilitate patient compliance by the use of a 28-day regimen where the patient takes a pill every day. Except for the nontherapeutic ferrous fumarate tablets, ESTROSTEP 21 and ESTROSTEP FE have the same therapeutic regimen.

ESTROSTEP 21 is listed in the Orange Book as a discontinued product. ESTROSTEP FE, currently named ESTROSTEP, remains on the list of currently marketed drug products.

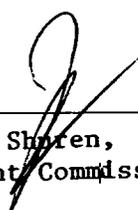
Barr Laboratories, Inc., submitted a citizen petition dated September 4, 2002 (Docket No. 2002P-0399/CP1), under 21 CFR 10.30 and § 314.161, requesting that FDA determine whether ESTROSTEP 21 tablets had been discontinued from sale for reasons of safety or effectiveness. In a letter dated December 1, 2004, Warner Chilcott confirmed to the agency that the firm never commercially marketed ESTROSTEP 21 in the United States. In previous instances (see the **Federal Register** of December 30, 2002 (67 FR 79640 at 79641) (addressing a relisting request for Diazepam Autoinjector)), FDA has concluded that, for purposes of §§ 314.161 and 314.162, never marketing an approved drug product is equivalent to withdrawing the drug from sale.

The agency has determined that ESTROSTEP 21 tablets, 0.02 mg/1 mg, 0.03 mg/1 mg, and 0.035 mg/1 mg, were not withdrawn from sale for reasons of safety or effectiveness. In support of this finding, we note that Warner Chilcott continues to market ESTROSTEP FE, which contains the same

therapeutic dosage regimen as ESTROSTEP 21. The petitioner identified no data or other information suggesting that ESTROSTEP 21 was withdrawn from sale as a result of safety or effectiveness concerns. FDA has independently evaluated relevant literature and data for possible postmarketing adverse event reports associated with this combination drug product and has found no information that would indicate this product was withdrawn from sale for reasons of safety or effectiveness.

After considering the citizen petition and reviewing agency records, FDA determines that for the reasons outlined in this document, ESTROSTEP 21 tablets, 0.02 mg/1 mg, 0.03 mg/1 mg, and 0.035 mg/1 mg, were not withdrawn from sale for reasons of safety or effectiveness. Accordingly, the agency will continue to list ESTROSTEP 21 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. ANDAs that refer to ESTROSTEP 21 may be approved by the agency as long as they meet all relevant legal and regulatory requirements for approval of ANDAs. If FDA determines that labeling for these drugs products should be revised to meet current standards, the agency will advise ANDA applicants to submit such labeling.

Dated: 5/15/07
May 15, 2007.



Jeffrey Shapiro,
Assistant Commissioner for Policy.

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Suzette Reese