

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2003P-0090]

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**Determination That SERZONE (Nefazodone Hydrochloride) Was 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Withdrawn From Sale for Reasons of Safety or Effectiveness**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SUMMARY: The Food and Drug Administration (FDA) has determined that SERZONE (nefazodone hydrochloride (HCl)) was not withdrawn from sale for reasons of safety or effectiveness. This determination means that FDA will not begin procedures to suspend approval of abbreviated new drug applications (ANDAs) for nefazodone HCl, and FDA may continue to approve ANDAs for nefazodone HCl.

FOR FURTHER INFORMATION CONTACT: Nicole Mueller, 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 a version of the drug that was 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 Under FDA regulations, drugs are withdrawn from the list if the agency withdraws or suspends approval of the drug’s NDA or ANDA for reasons of safety or effectiveness or if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (21 CFR 314.162).

Under § 314.161(a)(1) and (a)(2) (21 CFR 314.161(a)(1) and (a)(2)), the agency must determine whether a listed drug was withdrawn from sale for reasons of safety or effectiveness both before an ANDA that refers to that listed drug may be approved and if an ANDA referring to that listed drug has already been approved. FDA may not approve an ANDA that does not refer to a listed drug, and, under § 314.161(d), FDA must pursue suspension of approval for an ANDA if the agency determines the listed drug to which the ANDA refers was withdrawn for reasons of safety or effectiveness.

SERZONE (nefazodone HCl) is the subject of approved NDA 20–152 held by the Bristol-Meyers Squibb Co. (BMS). SERZONE is indicated for the treatment of depression. The Public Citizen Health Research Group (PCHRG) submitted a citizen petition to the agency, dated March 6, 2003, requesting that we immediately remove SERZONE from the market because of adverse events associated with the drug (cases of serious liver toxicity). On May 19,

2004, BMS announced that for commercial business reasons, particularly declining sales and increased generic competition, BMS would be discontinuing all sales and manufacture of SERZONE in the U.S. market effective June 14, 2004. Because of the potential for continued marketing of generic versions of nefazodone after BMS's withdrawal of SERZONE from sale, the issues raised in PCHRG's petition still warranted agency response. FDA responded to the petition in a letter dated June 14, 2004, denying the petition and explaining our reasons for concluding that the available data did not justify the agency's removal of nefazodone from the market. The agency also concluded, however, that the safe use of the drug could be improved through additional risk management measures, and BMS made changes to the product labeling to discourage the drug's use as a first-line drug (i.e., to encourage physicians to consider using other treatments first). The labeling for generic versions of nefazadone now must include these changes.

Having independently evaluated relevant literature and data, including from FDA's Adverse Event Reporting System, for possible postmarketing adverse event reports, FDA has now also determined, under § 314.161, that BMS's voluntary withdrawal from sale of SERZONE was not for reasons of safety or effectiveness. Accordingly, the agency will list SERZONE (nefazodone HCl) 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. Approved ANDAs that refer to the SERZONE

(nefazodone HCl) are unaffected by the withdrawal of SERZONE from the market. Additional ANDAs for nefazodone HCl may also be approved by the agency.

Dated: 10/15/04
October 15, 2004



Jeffrey Shuren
Assistant Commissioner for Policy

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