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DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Food and Drug Administration

[Docket No. 2006P–0520]

Determination That Methotrexate Injection, USP, Preservative Free, Equivalent to 500 Milligrams Base/20 Milliliters (25 Milligrams/Milliliter), Was Not Withdrawn From Sale for Reasons of Safety or Effectiveness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 methotrexate injection, USP, preservative free, equivalent to (Eq.) 500 milligrams (mg) base/20 milliliters (mL) (25 mg/mL), was not withdrawn from sale for reasons of safety or effectiveness. This determination will allow FDA to approve abbreviated new drug applications (ANDAs) for methotrexate injection, preservative free, Eq. 500 mg base/20 mL (25 mg/mL).

FOR FURTHER INFORMATION CONTACT: Elena Cohen, 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 applicants 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. ANDA applicants 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 (21 CFR 314.162).

Under 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.

Methotrexate injection, USP, preservative free, Eq. 500 mg base/20 mL (25 mg/mL), is the subject of approved NDA 11–719 currently held by Mayne Pharma USA (Mayne). Although NDA 11–719 was originally approved in 1959, this formulation and dosage was approved in April 2005 (S–108). Methotrexate is an antifolate cytotoxic drug used in the treatment of a variety of malignancies, including acute lymphoblastic leukemia, osteosarcoma, advanced metastatic breast cancer, and others. It is also used to treat some inflammatory conditions such as rheumatoid arthritis. To date, Mayne has not marketed methotrexate injection, USP, preservative free, Eq. 500 mg base/20

mL (25 mg/mL). At the request of the sponsor, the product was moved to the discontinued section of the Orange Book in June 2005. In previous instances (see, e.g., the **Federal Register** document of December 30, 2002 (67 FR 79640), addressing a relisting request for Diazepam Autoinjector), the agency has determined that, for purposes of §§ 314.161 and 314.162, never marketing an approved drug product is equivalent to withdrawing the drug from sale.

SICOR Pharmaceuticals, Inc., submitted a citizen petition dated December 15, 2006 (Docket No. 2006P–0520/CP1), under 21 CFR 10.30, requesting that the agency determine whether methotrexate injection, preservative free, Eq. 500 mg base/20 mL (25 mg/mL), was withdrawn from sale for reasons of safety or effectiveness. The petitioner has identified no data or other information suggesting that methotrexate injection, preservative free, Eq. 500 mg base/20 mL (25 mg/mL), was withdrawn from sale for reasons of safety or effectiveness. FDA has independently evaluated relevant literature and data for possible postmarketing adverse events and has found no information that would indicate this product was withdrawn for reasons of safety or effectiveness.

After considering the citizen petition and reviewing agency records, FDA has determined that, for the reasons outlined in this document, methotrexate injection, preservative free, Eq. 500 mg base/20 mL (25 mg/mL), was not withdrawn from sale for reasons of safety or effectiveness. Accordingly, the agency will continue to list methotrexate injection, preservative free, Eq. 500 mg base/20 mL (25 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. ANDAs that refer to methotrexate injection, preservative free, Eq. 500 mg base/20 mL (25 mg/mL), may be

approved by the agency as long as they meet all relevant legal and regulatory requirements for the approval of ANDAs. 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: July 30, 2007.

Randall W. Lutter,
Deputy Commissioner for Policy.

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