DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

DDM Display Date 2-27-04
Publication Date 3-1-04
Certifier R LEDESMA

[Docket No. 01P–0333]

Determination That Cytoxan (Cyclophosphamide for Injection), 2 Gram Vials (NDA 12–142 054), Was Not Withdrawn From Sale for Reasons of Safety or Effectiveness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 although Bristol Myers Squibb (Bristol) has discontinued marketing CYTOXAN, 2 gram (g) vials (cyclophosphamide for injection), this formulation was not withdrawn from sale for reasons of safety and effectiveness. As a result of this determination, approved abbreviated new drug applications (ANDAs) for cyclophosphamide for injection that referenced Bristol's cyclophosphamide for injection will not be removed from the market. Because Bristol has supplemented its CYTOXAN NDA and obtained approval for a new formulation, cyclophosphamide lyophilized, any unapproved ANDAs seeking to reference CYTOXAN as a reference listed drug must reference the currently approved formulation, cyclophosphamide lyophilized.

FOR FURTHER INFORMATION CONTACT: Howard P. Muller, Center for Drug Evaluation and Research (HFD–7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20855, 301–594–2041.

SUPPLEMENTARY INFORMATION: In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98–417)

N1

cd01143
20 01P-0333

(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 previously approved under a new drug application (NDA). Sponsors of ANDAs do not have to repeat the extensive clinical testing otherwise necessary to gain approval of an 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 § 314.162 (21 CFR 314.162), 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 voluntarily withdrawn from sale by the sponsor for reasons of safety or effectiveness.

Regulations also provide that 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 (§ 314.161(a)(1) (21 CFR 314.161(a)(1))). If the agency determines that a listed drug was withdrawn for reasons of safety or effectiveness, the drug must be removed from the list of approved drug products, and ANDAs referencing that drug may not be approved (§ 314.162). Under § 314.161(a)(2), the agency must also determine

whether a listed drug was withdrawn from sale for reasons of safety or effectiveness if ANDAs that referred to the listed drug have already been approved prior to its market withdrawal. If the agency determines that a listed drug was withdrawn from sale for reasons of safety or effectiveness, and there are approved ANDAs that reference that listed drug, FDA will initiate a proceeding to determine whether the suspension of the ANDAs is also required (21 CFR 314.153(b)).

On August 30, 1982, Bristol received approval for CYTOXAN (cyclophosphamide for injection), 2 g vials, under NDA 12–142 054. CYTOXAN is an alkylating agent used to treat various types of cancer. It interferes with the growth of cancer cells, which are eventually destroyed. On January 4, 1984, Bristol received approval for a new formulation of CYTOXAN, cyclophosphamide lyophilized, under NDA 12–142 058. Bristol's lyophilized formulation was approved on the basis of a showing of bioequivalence to the previously approved formulation. No additional clinical trials were required to demonstrate the safety or effectiveness of cyclophosphamide lyophilized. ANDAs were approved before the time the cyclophosphamide lyophilized formulation was approved. These ANDAs referenced cyclophosphamide for injection. Bristol discontinued marketing cyclophosphamide for injection, 2 g vials, in 1997. Cyclophosphamide for injection was moved from the prescription drug product list to the "Discontinued Drug Product List" section of the Orange Book in May 1997.

On July 26, 2001, ASTA Medica, Inc., submitted a citizen petition (Docket No. 01P–0333/CP1) to FDA under 21 CFR 10.30 requesting that the agency determine whether CYTOXAN, cyclophosphamide for injection, 2 g vials, was withdrawn from sale for reasons of safety or effectiveness. This determination

not only affects whether an ANDA may be submitted and approved under §§ 314.122 and 314.161 using CYTOXAN, cyclophosphamide for injection, 2 g, as the reference listed drug, but also affects whether the agency is required to initiate withdrawal proceedings for the ANDAs that reference cyclophosphamide for injection and were approved before its market withdrawal.

The agency has determined that Bristol did not withdraw cyclophosphamide for injection from sale for reasons of safety or effectiveness. Three grounds support the agency's finding. First, Bristol continues to market cyclophosphamide lyophilized (which is pharmaceutically and therapeutically equivalent to Bristol's withdrawn cyclophosphamide for injection) in a variety of strengths. FDA has no reason to believe that cyclophosphamide lyophilized has a different safety or effectiveness profile than cyclophosphamide for injection, and required Bristol to conduct no clinical trials (other than bioequivalence trials) to support the formulation change. Second, the petitioner identified no adverse event data or other information suggesting that Bristol withdrew cyclophosphamide for injection from sale as a result of safety or effectiveness concerns. Third, FDA has independently evaluated relevant literature and internal agency data for possible postmarketing reports associated with cyclophosphamide for injection, 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 its records, FDA determines that, for the reasons outlined above, Bristol's cyclophosphamide for injection was not withdrawn from sale for reasons of safety or effectiveness.

Thus, FDA will not initiate proceedings to suspend the approvals of ANDAs referencing cyclophosphamide for injection. However, because Bristol has

2/20/04

supplemented its CYTOXAN NDA and obtained approval for a new formulation, cyclophosphamide lyophilized, any unapproved ANDAs seeking to reference CYTOXAN (NDA 12–142 054) must reference the currently approved formulation.

Dated: 2/15/04

February 15, 2004.

Jeffrey Shuren,
Assistant Commissioner for Policy.

[FR Doc. 04–????? Filed ??–??–04; 8:45 am]

BILLING CODE 4160–01–S

CERTIFIED TO BE A TRUE
COPY OF THE ORIGINAL