NDA 50-718/S-006

ALZA Corporation
Attention: Janne Wissel
Sr. Vice President, Operations
950 Page Mill Road
P.O. Box 10950
Palo Alto, CA 94303-0802

Dear Ms. Wissel:

Please refer to your supplemental new drug application dated December 23, 1998, received December 29, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Doxil® (doxorubicin HCl liposome injection).

We acknowledge receipt of your submissions dated January 27, February 11 and 24, March 3 and 31, April 20 and 22, June 17, 21, and 25, 1999.

This supplemental new drug application provides for the use of Doxil (doxorubicin HCl liposome injection) for the treatment of metastatic carcinoma of the ovary in patients with disease that is refractory to both paclitaxel- and platinum-based chemotherapy regimens. Refractory disease is defined as disease that has progressed while on treatment, or within 6 months of completing treatment.

We have completed the review of this supplemental application, as amended, according to the regulations for accelerated approval, and have concluded that adequate information has been presented to approve Doxil (doxorubicin HCl liposome injection) for use as recommended in the enclosed labeling text. Accordingly, the supplemental application is approved under 21 CFR Subpart H. Approval is effective on the date of this letter. Marketing of this drug product and related activities are to be in accordance with the substance and procedures of the referenced accelerated approval regulations.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 50-718/S-006." Approval of this submission by FDA is not required before the labeling is used.

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies to verify and describe clinical benefit. We remind you of your post marketing study 30-49 entitled, "A Phase 3, Randomized, Open-Label, Comparative Study of Doxil/CAELYX versus Topotecan HCl in Patients with Epithelial Ovarian Carcinoma Following Failure of First-Line, Platinum-Based Chemotherapy" and your commitments agreed upon in your submission dated June 25, 1999. These commitments, along with the completion dates agreed upon, are listed below.

> You agree to provide data from the interim analysis of study 30-49 by July 12, 1999, and the final study analysis by the week of March 31, 2000.
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> If after review and discussion of the data with you, we believe that the results demonstrate convincing superiority of Doxil over topotecan HCl in either time to progression (TTP) or survival, with a supporting trend demonstrated for the other endpoint, then this would likely fulfill the Phase 4 requirement for demonstrating clinical benefit. In that case, you agree to submit a supplemental NDA within 6 months.
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> If the results of study 30-49 do not demonstrate the clinical benefit of Doxil, you agree to submit a protocol for a study designed to prove the clinical benefit of Doxil in ovarian cancer and a proposed timetable for completion and submission of the study. The protocol and timetable will be submitted within one month of the meeting with the Agency at which the results of this study are discussed.

Final study reports should be submitted to this NDA as a supplemental application. For administrative purposes, all submissions relating to this Phase 4 commitment must be clearly designated "Subpart H Phase 4 Commitments."

In addition, we note your following Phase 4 commitment, specified in your submission dated June 25, 1999, that is not a condition of the accelerated approval. This commitment provides for:

> Submission of complete clinical pharmacokinetic data for verification by the Agency and incorporation into the package insert, as appropriate. This data should be submitted within 45 days of the action letter date.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

We also remind you that, under 21 CFR 314.550, after the initial 120 day period following this approval, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Alvis Dunson, Project Manager, at (301) 594-5750.

Sincerely,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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