

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 21174

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-174

MAY 17 2000

Wyeth-Ayerst
Attention: Maureen D. Skowronek
Director, U.S. Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Ms. Skowronek:

Please refer to your new drug application (NDA) dated and received October 29, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mylotarg (gemtuzumab ozogamicin) for Injection.

We acknowledge receipt of your submissions dated December 13, 21, 23, 30, 1999 and January 27(2), February 14, 23, March 7, 15(2), 28, 31(2), and April 6, 7, 13, 20 21(3), 27(2) and 28, 2000.

Mylotarg is indicated for the treatment of patients with CD33 positive acute myeloid leukemia in first relapse who are 60 years of age or older and who are not considered candidates for cytotoxic chemotherapy.

We have completed the review of this application, as amended, according to the regulations for accelerated approval, and have concluded that adequate information has been presented to approve Mylotarg (gemtuzumab ozogamicin) for Injection for use as recommended in the enclosed labeling text. Accordingly, the 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.

Products approved on the basis of an effect on a surrogate endpoint reasonably likely to predict a clinical benefit (in this case an effect on CR and CRp), under the accelerated approval regulations, 21 CFR 314.510, may require further adequate and well-controlled studies to verify and describe the clinical benefit. We remind you of your post-marketing study commitment specified in your submission dated May 3, 2000. This commitment is stated below.

A randomized controlled trial of gemtuzumab ozogamicin, daunorubicin and cytarabine versus daunorubicin and cytarabine as induction therapy in patients with *de novo* CD33-positive acute myeloid leukemia. This trial should be

designed to demonstrate superior survival in the three-drug (gemtuzumab ozogamicin containing) group. Response rate results can be used as supportive evidence; responses should be defined as CR's or CRp's of at least 4 weeks duration. If the three-drug regimen cannot be designed with acceptable toxicity, a randomized controlled trial designed to show that survival in patients treated with gemtuzumab ozogamicin and cytarabine is not inferior to survival in patients given daunorubicin and cytarabine should be initiated following discussion with the division. Again, the definition of the supportive secondary end point, response (CR and CRp), should include a pre-specified minimum duration of response of 4 weeks.

For either randomized trial it will be necessary to:

- a. Clarify the purpose and the number of interim analyses planned, adjusting type I error as necessary. An independent, expert data monitoring committee will review bone marrow results, conduct the interim analyses, and make recommendations regarding continuation of the study. Responses should be determined by an independent pathologist blinded to the treatment arm.
- b. Pre-specify subgroups and covariates that are likely to be used in the analyses. The relationship of CD33 quantitative expression to response should be examined.
- c. Perform a thorough evaluation of toxicity, both hematologic and non-hematologic, in patients undergoing subsequent post-remission therapy such as hematopoietic stem cell transplantation or high dose cytarabine, as well as in patients who receive no further therapy.
- d. Perform long-term follow-up for relapse and survival in patients following post-remission therapy, as well as for patients who receive no further therapy.
- e. Perform the appropriate phase 1 trials to ensure that the toxicities observed with the dose combinations in the above trials are acceptable; and to identify any potentially significant pharmacokinetic drug-drug interactions.

The final study report for the selected randomized trial 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 that you have agreed to conduct the following post-marketing study, described in your submissions dated April 20, 27, 28 and May 3, 2000.

You have reported multiple metabolites of CMA-676 in your NDA submission but the metabolism of CMA-676 is not described, therefore, you will identify the enzymes involved in the metabolism of CMA-676. Depending upon the pathways found to be involved, we may ask for additional studies of possible drug-drug interactions.

We note that in your submissions dated April 20 and 27, 2000, you have agreed to:

1. Examine the pharmacokinetic data collected from all trials to explore the possibility that various patient characteristics (demographic, clinical status) affect total and unconjugated calicheamicin pharmacokinetics.
2. Analyze the pharmacokinetic data for total and unconjugated calicheamicin for study 203 and studies 201 and 202 providing a comparison of pharmacokinetics in patients under 60 years and patients 60 years of age or older.
3. Provide a detailed description of the test methods used for analyzing the strength and purity of []
4. Develop a specification for assay of unconjugated antibody.

Although orphan drugs are exempt from the requirements of the pediatric rule []

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

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 heavyweight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-174." Approval of this submission by FDA is not required before the labeling is used.

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.

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Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

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, call Sean Bradley, Project Manager, at (301) 594-5750.

Sincerely,

/S/

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

Enclosure