CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103948/0

APPROVABLE LETTER 2

Our STN: BL 103948/0

FEB 2 0 2001

Jacqueline J. Cinicola
Millennium & ILEX Partners, LP
75 Sidney Street
Cambridge, MA 02139

Dear Ms. Cinicola:

This letter is in regard to your biologics license application for Alemtuzumab submitted under section 351 of the Public Health Service Act. Reference is also made to our complete response letter dated June 23, 2000, and your response dated August 21, 2000.

The Center for Biologics Evaluation and Research (CBER) has completed the review of all submissions made relating to this application. Our review finds that the information and data submitted are inadequate for final approval action at this time based on the deficiencies outlined below.

As requested in your amendment of February 13, 2001, marketing approval for this product is being sought under the accelerated approval regulations for biological products, 21 CFR 601.40-46. These regulations permit the use of certain surrogate endpoints or an effect on a clinical endpoint other than survival or irreversible morbidity as the basis for approval of products intended for serious or life-threatening illnesses or conditions.

Among other things, approval under these regulations requires that you conduct adequate and well-controlled studies to verify and describe clinical benefit as evidenced by durable favorable outcomes and to verify the contribution of Alemtuzumab to these outcomes, and that such studies be carried out with due diligence. We have reviewed your draft proposals for a confirmatory clinical study submitted on January 25, 2001, and February 12, 2001, and have the following comments:

1. Please submit a protocol for a confirmatory study that addresses the issue of relative activity and toxicity of Alemtuzumab versus an alternative agent in patients with chronic lymphocytic leukemia. As discussed with CBER during the February 15, 2001, telephone conference, this confirmatory study should be designed as a comparison of single agent Alemtuzumab to an acceptable active control, e.g. single agent fludarabine.

2. Please submit a proposed schedule for conducting the confirmatory study, including all major milestones for the study, e.g. completion of patient accrual, completion of the study, and submission of the final study report, SAS datasets, and applicable revised labeling to the FDA.

As discussed during the February 15, 2001, telephone conversation, we acknowledge your verbal commitments to conduct additional post-marketing studies. Relevant to these studies, we request the following:

3. Please submit a protocol to study the effect of Alemtuzumab therapy on the responses to vaccinations for infectious diseases.

4. Please submit a protocol to determine the incidence of loss of CD52 (i.e., the emergence of CD52 negative clones) following treatment with Alemtuzumab in patients being considered for a second course of Alemtuzumab. The proposal also should include details of the assay methodology for CD52 expression on leukemic cells.

Please submit written confirmation of these commitments and describe your plans to address comments 3 and 4 in sufficient detail to permit our evaluation of the adequacy of the proposals. We request that your response include:

- A detailed protocol describing all design features of the study including sample size and justification, eligibility criteria with rationale, dosing regimens and duration, clinical assessments to be performed and their timing, and endpoints to be analyzed.

- Proposed schedule for conducting the study, including all major milestones for the study, e.g. completion of patient accrual, completion of the study, and submission of the final study report, SAS datasets, and applicable revised labeling to the FDA.

Please be advised that submission of complete protocols for review and comment should be made to your IND and may be cross-referenced in your response to this letter.

5. Protocol CAM213, submitted to IND 4294 on January 19, 2001, is adequate to address the issue of characterization of the pharmacokinetic profile of Alemtuzumab at the approved dose and schedule in patients with chronic lymphocytic leukemia. Please submit a proposed schedule for conducting the study, including all major milestones for the study, e.g. completion of patient accrual, completion of the study, and submission of the final study report, SAS datasets, and applicable revised labeling to the FDA.

6. Comments on your proposed package insert are enclosed. Please submit revised draft labeling that includes our requested changes.

You may request a meeting or teleconference with CBER to discuss the steps necessary for approval. Should you wish to have such a meeting, please submit your meeting request as

described in the FDA Guidance for Industry: Formal Meetings with Sponsors and Applicants for PDUFA Products - February, 2000 (http://www.fda.gov/cber/gdlns/mtpdufa.pdf).

Within 10 days after the date of this letter, you are requested to take one of the following actions: (1) amend the application; (2) notify us of your intent to file an amendment; (3) withdraw the application; or (4) request an opportunity for a hearing on the question of whether there are grounds for denying approval of the application. In the absence of any of the above responses, CBER may initiate action to deny the application.

Please note our review clock has been suspended with the issuance of this letter. Note also that any amendment should respond to all deficiencies listed and that a partial reply will not be considered for review nor will the review clock be reactivated until all deficiencies have been addressed.

Should you need additional information or have any questions concerning administrative or procedural matters please contact the Regulatory Project Manager, Ms. Sharon Sickafuse, in the Division of Application Review and Policy at (301) 827-5101.

Sincerely yours,

Karen D. Weiss, M.D.
Director
Division of Clinical Trial Design
and Analysis
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

Kathryn E. Stein, Ph.D.
Director
Division of Monoclonal
Antibodies
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

Enclosure: Revised package insert

cc: HFM-515/P. Harris
HFM-555/K. Webber
HFM-555/K. Stein
HFM-561/K. Brorson
HFM-110/RIMS
HFM-500/S. Risso
HFM-500/J. Siegel
HFM-585/G. Jones
HFM-588/S. Sickafuse
HFM-570/K. Weiss
HFM-570/P. Keegan
HFM-573/G. Schechter
HFM-579/M. Green
HFM-215/C. Gnecco
HFM-650/L. Johnson
HFM-675/W. Lange

OTRR:DARP:Sickafuse:2-13-01:2-14-01:2-15-01:Dixon:2.20.01
(S:/Sickafuse/Campath/CR letter.2.doc

MILESTONE: COMPLETE RESPONSE LETTER - (RL)

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
DARP	Sickafuse	2-20-01				OTRR	R. [illegible] for K. Weiss	20 Feb 01
DARP	[illegible]	2-20-01	DMA	Stein	2/20/01	DARP	A. Williams	2-20-01
DARP	Dye for G. Jones	2-20-01	DMA	Stein for Brorson	2/20/01			