

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 21055

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-055

DEC 29 1999

Ligand Pharmaceuticals Incorporated
10275 Science Center Drive
San Diego, California 92121-1117

Attention: Howard T. Holden, Ph.D.
Vice President
Regulatory Affairs and Compliance

Dear Dr. Holden:

Please refer to your new drug application (NDA) dated June 22, 1999, received June 23, 1999, and submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Targretin® (bexarotene) capsules, 75 mg.

We acknowledge receipt of your submissions dated December 23 and 28, 1999. Your submission of December 23, 1999 constituted a complete response to our December 23, 1999 action letter.

This new drug application provides for the use of Targretin® (bexarotene) capsules for the treatment of cutaneous manifestations of cutaneous T-cell lymphoma in patients who are refractory to at least one prior systemic therapy.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient 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 heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-055." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitments specified in your submission dated December 23 and 28, 1999. These commitments, along with any completion dates agreed upon, are listed below.

1. To conduct a randomized controlled clinical trial in patients with cutaneous T-cell lymphoma. The trial should compare three dose levels of Targretin. We agree with your proposed doses of 125, 300 and 400 mg/m². The primary endpoint should be tumor response according to the Physician's Global Assessment, the Composite Assessment of Index Lesion Severity and the percent Body Surface Area Involvement with tumor. Tumor responses must be documented with photographs of index lesions and full body photographs (front and back). Time to tumor response, time to tumor progression and tumor response duration should also be assessed. The effect on pruritis and other tumor specific symptoms should be assessed. The trial must be conducted in the same patient population for which the drug is approved. Quality of life should also be assessed. Agreed upon dates for this trial are as follows: the trial should be initiated with 3 months of protocol finalization; patient accrual should be completed 3.5 years after study initiation; the study results and analysis should be submitted to the Agency within 9 months of the date that all patients remaining on the study have been followed for at least 24 weeks. Bone mineral density testing will be conducted in a cohort of these study patients.
2. A phase 4 drug-drug interaction study, in patients or healthy subjects (sampling of sufficient frequency to describe potential multi-exponential pharmacokinetics and of sufficient duration to describe elimination half-life), characterizing the pharmacokinetics of bexarotene when ketoconazole is co-administered with Targretin®.
3. Phase 4 *in vitro* studies to determine the inhibition potential bexarotene on cytochrome enzymes. The results of these studies may indicate that it is necessary to perform subsequent *in vivo* studies if CDER review of the *in vitro* data indicates that such studies are essential.
4. To determine with greater accuracy and precision if:
 - There are pharmacokinetic differences between elderly and non-elderly.
 - There are pharmacokinetic differences between males and females.
 - There are pharmacokinetic differences between ethnic groups.

There are two methods that could be used to accomplish these determinations. An independent prospective study in the appropriate groups can be conducted. Alternatively, a prospectively planned scheme of plasma sampling in the agreed to Phase 4 clinical

study combined with the data acquired to date and a formal population PK analysis (NONMEM or other similar tool) could be used.

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."

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.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Oncology Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

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.

NDA 21-055

Page 4

If you have any questions, call Amy Chapman, Consumer Safety Officer, at (301) 594-5771.

Sincerely,

A handwritten signature in black ink, appearing to read "RST", with a small dot to the right.

Robert Temple, M.D.

Director

Office of Drug Evaluation I

Center for Drug Evaluation and Research

Enclosures