DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-863

JAN 15 1999

Otsuka Pharmaceutical Company, Ltd
c/o Otsuka America Pharmaceutical, Inc.
Attention: Tanveer Ahmad, Ph.D.
2440 Research Boulevard
Rockville, MD 20850

Dear Dr. Ahmad:

Please refer to your new drug application (NDA) dated September 19, 1997, received September 19, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pletal (cilostazol) 50 and 100 mg Tablets.

We acknowledge receipt of your submissions dated September 24, 29, and 30, October 2, 14, and 19, November 9 (two), 10, 16, and 30, and December 8, 11, and 22, 1998.

This new drug application provides for the use of Pletal (cilostazol) 50 and 100 mg Tablets for the reduction of symptoms of intermittent claudication.

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 labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed package insert and patient package insert must be identical to the enclosed marked-up drafts. The final printed immediate container and carton labels submitted November 30, 1998 are acceptable and need not be resubmitted. 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 final printed package insert and patient package insert as soon as they are available, in no case more than 30 days after they are 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 20-863." 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 November 9, 1998. These commitments, along with any completion dates agreed upon, are listed below.

You have committed to conduct studies to determine the effect of ketoconazole and the effect of grapefruit juice administration on the pharmacokinetics of cilostazol. Protocols for these studies will be submitted to the Division during the first quarter of 1999.

In addition, you have committed to conduct a trial to understand better the risk, if any, of long-term use of Pletal. This trial will compare the effects of Pletal with those of pentoxifylline and placebo in about 1800 intermittent claudication patients of any severity (including patients on clopidogrel). Efficacy will be monitored for the first 3-6 months and safety will be monitored for a total of 12 months. The exact details of the protocol will be submitted to the Division during the first quarter of 1999. The study will start during the second quarter of 1999; the final report will be submitted six months after completion of the study. A concentrated effort should be made to include a significant fraction of patients on clopidogrel in this trial.

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 314.81(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.

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, please contact:

Mr. Gary Buehler
Regulatory Health Project Manager
(301) 594-5332

Sincerely yours,

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

Enclosure