DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-743

OSI Pharmaceuticals Inc.
Attention: Christine Boisclair
Senior Director, Global Regulatory Affairs
58 South Service Road, Suite 110
Melville, NY 11747

Dear Ms. Boisclair:

Please refer to your new drug application (NDA) dated July 29, 2004, received July 30, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tarceva (erlotinib) tablets, 25 mg, 100 mg and 150 mg.

We acknowledge receipt of your submissions dated January 20, March 31, May 5, 6, 12, 19, 24, June 3, 22, 24, 28, July 7, 29, August 3, 6, 18, 20, 30, September 1, 3, 13, 14, 15, 17, October 11, 14, 19, 20, 26, 29, November 3, 7, 9 and 11, 2004.

This new drug application provides for the use of Tarceva (erlotinib) tablets for treatment of locally advanced or metastatic Non Small-Cell Lung Cancer (NSCLC) after failure of at least one prior chemotherapy regimen.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling text and submitted labeling (immediate container and carton labels submitted October 14, 2004). Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-743**." Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

We remind you of your postmarketing study commitments in your submissions dated October 26, 2004 and November 16, 2004. These commitments are listed below.

1. STUDY DESCRIPTION: A double-blind randomized Phase 3 study to evaluate the efficacy of Tarceva or placebo following 4 cycles of platinum-based chemotherapy in patients with histologically documented advanced or recurrent (stage IIIB and not amenable for combined modality treatment) or metastatic (Stage IV) non-small cell lung cancer (NSCLC) who have not experienced disease progression or unacceptable toxicity during chemotherapy. The primary endpoint will be PFS. The study will also be sized to detect a realistic difference in survival. For eligibility all patients must have EGFR expression status determined by Dako Kit prior to randomization. Analyses of results will include assessment of treatment effect in the subgroup with EGFR expression status positive and the subgroup with EGFR expression status negative.

   Protocol submission date: March, 2005
   Study Start: June, 2005
   Final Report Submission: December, 2008

2. STUDY DESCRIPTION: A randomized Phase 3 study to evaluate the efficacy of Tarceva or chemotherapy (Alimta or Taxotere) following 4 cycles of platinum-based chemotherapy in patients with histologically documented advanced or recurrent (stage IIIB and not amenable for combined modality treatment) or metastatic (Stage IV) non-small cell lung cancer (NSCLC) who have experienced disease progression or unacceptable toxicity during chemotherapy. The primary endpoint will be overall survival (subject to FDA agreement during SPA review). For eligibility all patients must have EGFR expression status determined by Dako Kit prior to randomization. Analyses of results will include assessment of treatment effect in the subgroup with EGFR expression status positive and the subgroup with EGFR expression status negative.

   Protocol submission date: March, 2005
   Study Start: June, 2005
   Final Report Submission: December, 2008

3. OSI agrees to conduct a study to determine the pharmacokinetics of erlotinib in hepatically-impaired cancer patients.

   STUDY DESCRIPTION: The first phase will consist of an open label, single dose parallel group PK study of Tarceva in male and female cancer patients. Group A will consist of cancer patients with normal hepatic function. Group B will consist of cancer patients with hepatic insufficiency that falls into the Child Pugh score of moderate impairment (Child Pugh B). Based on the 50% CV observed for erlotinib plasma AUC and Cmax in patients, a minimum of 17 patients is required in each group in order to have 80% power to detect a 50% difference between groups. The power of this analysis may be reduced if the interpatient variability in hepatic impaired patients is greater than in patients with normal hepatic function. If a significant difference is not observed between groups after this first phase, the Phase 4 commitment will have been satisfied and further studies in hepatic impairment will not be conducted. If a significant difference is observed between the two groups, the population estimates for PK will be determined and simulations used to choose a dose adjustment strategy that will be discussed with the FDA before proceeding to the second phase.

Protocol submission date: February 2005
Study Start: May 2005
Final Report Submission: February 2007

4. OSI agrees to conduct a study to assess the ability of dose adjustment to compensate for the large decrease in erlotinib AUC seen when TARCEVA is co-administered with a strong enzyme inducer.

   STUDY DESCRIPTION: Population PK analysis will be performed on the data from the existing study (NP16638) which compared erlotinib PK in healthy male subjects who were administered rifampicin over a 7 day period prior to a single 150 mg dose of Tarceva, to the erlotinib PK following a single 150 mg dose of Tarceva in subjects who did not receive rifampicin. An adjusted dose of Tarceva will be determined for subjects receiving rifampicin that would result in comparable erlotinib plasma exposure, and the study repeated to evaluate the impact of the dose adjustment on erlotinib exposure.

   Protocol submission date: February 2005
   Study Start: May 2005
   Final Report Submission: November 2005

5. OSI agrees to completion of the ongoing midazolam drug interaction study.

   Protocol submission date: Study already ongoing
   Study Start: Study already ongoing
   Final Report Submission: December 2005

6. OSI agrees to explore the contribution of non-CYP routes to the metabolism of erlotinib by conducting a review of the in vitro CYP metabolism studies submitted with the NDA filing and evaluating whether additional calculations based on these studies will clarify the contribution of CYPs to the overall clearance of erlotinib.

   Any additional insights obtained from this effort will be submitted to the FDA by December 15, 2004 for discussion. Based on the review by the FDA, we would then propose any additional studies that may be required to address the metabolism of erlotinib.

   Protocol submission date (if required): February 2005
   Study Start: May 2005
   Final Report Submission: November 2005

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled

"**Postmarketing Study Protocol**", "**Postmarketing Study Final Report**", or "**Postmarketing Study Correspondence**."

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Paul Zimmerman, Regulatory Project Manager, at (301) 594-5775.

Sincerely,

{See appended electronic signature page}

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

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Temple

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