



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-743/S-008/S-010

OSI Pharmaceuticals, Inc.
Attention: Christine Boisclair
Vice President, Global Regulatory Affairs
41 Pinelawn Road
Melville, NY 11747

Dear Ms. Boisclair:

Please refer to your supplemental new drug application, S-008, dated October 16, 2006, received October 17, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tarceva (erlotinib) Tablets.

We acknowledge receipt of your submissions dated May 16, 2007 and July 2 and August 18, 2008.

Your supplemental new drug application, S-008, is superseded by your supplemental new drug application, S-010. [REDACTED]

Please also refer to your supplemental new drug application, S-010, dated September 7, 2007, received September 10, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tarceva (erlotinib) Tablets.

We acknowledge receipt of your submissions dated February 26, 28, March 19, April 4, May 20, June 11, 26, July 2, and August 18, 2008.

This supplemental new drug application provides for changes to the Clinical Pharmacology, Warnings, Precautions, Adverse Reactions, and Dosage and Administration sections of the package insert.

We completed our review of this application, as amended. This application 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 (agreed upon text for the package insert).

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 supplement NDA 21-743/S-010.**" Approval of this submission by FDA is not required before the labeling is used.

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the enclosed labeling (text for the package insert). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 21-743/S-010."

We refer to your postmarketing study commitments acknowledged in our November 18, 2004 letter. We have received your submission dated September 6, 2007, reporting on the following postmarketing study commitment.

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

We have reviewed your submission and conclude that the above commitment was fulfilled.

We also remind you of the following postmarketing study commitments acknowledged in our November 18, 2004 letter. 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

This commitment is open.

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

This commitment is open.

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
Status: Submitted

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 Commitment Protocol**”, “**Postmarketing Study Commitment Final Report**”, or “**Postmarketing Study Commitment 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:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

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

If you have any questions, call Paul Zimmerman, Regulatory Project Manager, at 301-796-1489.

Sincerely,

{See appended electronic signature page}

Robert Justice, M.D.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

**This is a representation of an electronic record that was signed electronically and
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/s/

Robert Justice
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