DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21743

REVISED WRITTEN REQUEST
AMENDMENT 1

OSI Pharmaceuticals, LLC
Attention: Derek Williams
Senior Director, Regulatory Affairs
Astellas Pharma Global Development, Incorporated
1 Astellas Way
Northbrook, IL 60062

Dear Mr. Williams:

Please refer to your correspondence dated June 12, 2014, requesting changes to FDA's May 7, 2010 Written Request issued under IND 53728 for pediatric studies for Tarceva (erlotinib).

We have reviewed your proposed changes and are amending the below-listed section of the Written Request. All other terms stated in our Written Request issued on May 7, 2010 remain the same. (Text added is underlined. Text deleted is ~~strikethrough~~.)

> *Timeframe for submitting report of the study:* Report of the above study must be submitted to the Agency on or before ~~June 30, 2014~~ December 31, 2014. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study report is submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the report of the study at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated May 7, 2010, and as amended by this letter must be submitted to the Agency on or before December 31, 2014, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to the approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC**

STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission, via fax (240-276-9327) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773.

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

- the type of response to the Written Request (i.e., complete or partial response);
- the status of the application (i.e., withdrawn after the supplement has been filed or pending);
- the action taken (i.e., approval, complete response); or
- the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

If you have any questions, call Dr. Mona Patel, Regulatory Project Manager, at 301-796-4236.

Sincerely,

{See appended electronic signature page}

Gregory Reaman, M.D.
Associate Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Complete Copy of Written Request as Amended

- *Type of studies*:
  Pharmacokinetic (PK) Studies: Studies and/or analyses, including pharmacokinetics that defines age appropriate dosing in pediatric patients.

  Phase 2 Study: An open-label, multi-center, randomized phase 2 trial evaluating the safety, efficacy and pharmacokinetics of erlotinib and etoposide (active comparator) utilizing a 1:1 randomization scheme.

  These studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Indication(s) to be studied:*
  PK Studies: pediatric patients with cancer.
  Phase 2 Study: pediatric patients with recurrent ependymoma.

- *Age group in which study will be performed*:
  PK Studies: Patients 3 to 21 years of age.
  Phase 2 Study: Patients $\geq$1 year to $\leq$ 21 years of age at randomization.

- *Number of patients to be studied:*
  PK Studies: The number of patients entered must be sufficient to achieve Phase 1 objectives.
  Phase 2 Studies: at least 40 (at least 20 per erlotinib arm; at least 20 per etoposide arm)

- *Study endpoints*
  PK Studies:
  1. Determine the maximum tolerated dose (MTD), dose-limiting and other toxicities in pediatric patients with cancer

  Phase 2 Study:
  1. Primary: Objective response rate (ORR) as assessed by investigator.
  2. Secondary: Duration of response, progression-free survival (PFS), and overall survival (OS)

  All Studies: Pharmacokinetic samples must be collected through approaches such as rich sampling or optimal sparse sampling in patients. Such data must then be appropriately analyzed using methods such as nonlinear mixed effects modeling or noncompartmental analysis. Available Phase 1 data and the data from the Phase 2 trial must be combined to develop pharmacokinetic and pharmacodynamic (PK-PD) models to explore exposure-response relationships for measures of safety and effectiveness. The pharmacokinetic studies must be prospectively powered to target a 95% confidence interval within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution for erlotinib in each of the age groups (1-6, 7-16 years old).

- *Drug information:*

  - *Dosage Form:*
    PK Studies: Oral solution, whole tablets and/or crushed tablets.

Phase 2 studies: Tablets crushed in apple sauce.

- *Route of Administration:* Oral

- *Regimen:*
  PK Studies: Erlotinib 35-160 mg/m^2/day continuously
  Phase 2 Study: Erlotinib 85 mg/m^2/day continuously

Use an age-appropriate formulation in the studies described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

If 1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives marketing approval), 2) the Agency publishes the exclusivity determination notice required under section 505A(e)(1) of the Act, and 3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice reflecting the fact that the approved pediatric formulation has not been marketed, in accordance with section 505A(e)(2).
If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

- *Drug specific safety concerns*: In clinical trials with adults, rash (dermatosis), diarrhea, nausea, fatigue, stomatitis, vomiting, and headache were the most frequently observed undesirable effects following exposure to single-agent erlotinib.

- *Statistical information, including power of study and statistical assessments:*

  PK Studies: Descriptive statistics.

  Phase 2 Study:

  All randomized patients will be included in the efficacy analysis. Following the intent-to-treat principle, patients will be analyzed according to the treatment to which they were assigned at randomization.

The ORR along with exact 95% confidence intervals will be calculated for each treatment arm. In addition, the ORR between the 2 treatment arms will be compared using Fisher's exact test. Assuming ORR is between 10% and 40% for single-agent erlotinib, the power for the final analysis of ORR using Fisher's exact test (alpha = 0.05, two-sided) is no more than 12% with the current sample size (20 patients per arm).

With 20 patients in each arm, the chance to observe at least 1 responder in each arm will be 64%, 88%, 96%, and 99% if the true response rate in each arm is 5%, 10%, 15%, and 20%, respectively. If the response rate is at least 15% in each arm, the chance of not observing any responder in each arm is less than 5%.

The study has been designed to consider stopping early at an interim analysis due to lack of efficacy, minimizing additional patient exposure to treatment that is unlikely to provide benefit.

There will be two interim analyses: the first will occur when the first 10 patients in the erlotinib arm have had at least 1 scheduled radiological assessment and the second will occur when the first 10 patients in the erlotinib arm have had at least 2 scheduled radiological assessments. The criteria for lack of efficacy have been strictly defined.

The lack of efficacy for the first interim analysis is defined as follows:

- $\geq$ 7 of the 10 patients in the erlotinib arm have PD; and
- No response [complete response (CR) or partial response (PR)] or minor response in the erlotinib arm; and
- $\geq$ 1 response (CR, PR) in the etoposide arm.

The lack of efficacy for the second interim analysis is defined as following:

- All 10 patients in the erlotinib arm have progressive disease (PD); and
- $\geq$ 1 response (CR, PR) in the etoposide arm.

Time to event variables (PFS or OS) will be analyzed by constructing Kaplan-Meier curves for each treatment arm. Median time to event and 95% confidence intervals will be estimated from the Kaplan-Meier curve. The treatment effect of erlotinib relative to etoposide will be analyzed using log-rank test. The corresponding hazard ratio of the treatment effect along with 95% confidence intervals will be calculated using a Cox proportional hazard model.

- *Labeling that may result from the study*: You must submit proposed pediatric labeling to incorporate the findings of the study. Under section 505A(j) of the Act, regardless of whether the study demonstrate that erlotinib is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study. Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study.

- *Format and types of report to be submitted*: You must submit full study report (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the report must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or

White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

Under section 505A(d)(2)(B) of the Act, when you submit the study report, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. These postmarketing adverse event reports should be submitted as narrative and tabular reports.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/Cder/guidance/7087rev.htm.

Timeframe for submitting report of the study: Report of the above study must be submitted to the Agency on or before December 31, 2014. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study report is submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the report of the study at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

Response to Written Request: Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric study will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study. If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Furthermore, if you agree to conduct the study, but have not submitted the study report on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

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

/s/

GREGORY H REAMAN
06/23/2014