CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

022405Orig1s000

Trade Name: No Trade Name

Generic Name: vandetanib tablets, 100 mg and 300 mg.

Sponsor: AstraZeneca Pharmaceuticals LP

Approval Date: April 6, 2011

Indications: Treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease. Use of vandetanib in patients with indolent, asymptomatic or slowly progressing disease should be carefully considered because of the treatment related risks of vandetanib.

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022405

NDA APPROVAL

AstraZeneca Pharmaceuticals LP
Authorized US Agent for iPR Pharmaceuticals, Inc.
Attention: Debra N. Shiozawa, Ph.D.
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Dr. Shiozawa:

Please refer to your New Drug Application (NDA) dated July 7, 2010, received July 7, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for vandetanib tablets, 100 mg and 300 mg.

We acknowledge receipt of your amendments dated July 7, 12, and 27, 2010; August 3 (2), 4, 13 (2), 18, 20, 24, and 25 (2), 2010; September 9, 10, 13, 17, 22, and 29, 2010; October 8, 15, 18, 19 (2), 22, and 27, 2010; November 3, 4, 9, 10 (2), 17 (2), 18, 23, and 30 (2), 2010; December 7, 17, 20, 21, and 22 (2), 2010; January 19, 25, and 26, 2011; February 10, and 17, 2011; and March 3, 8 (2), 10, 18, 22 (2), 23 and 24, 2011; April 6, 2011.

This new drug application provides for the use of vandetanib 100 mg and 300 mg tablets for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease. Use of vandetanib in patients with indolent, asymptomatic or slowly progressing disease should be carefully considered because of the treatment related risks of vandetanib.

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 and with the minor editorial revisions: deleting commas, italicizing, and spacing of typographically conjoined words.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the

Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your March 23, 2011, submission containing final printed carton and container labels.

PROPRIETARY NAME

If you choose to use a proprietary name for this product, the name and its use in the labels must conform to the specifications under 21 CFR 201.10 and 201.15. We acknowledge your submission dated March 18, 2011 requesting a proprietary name review for vandetanib. Should your proprietary name be acceptable, you will need to submit proposed labeling and a REMS modification that incorporates the accepted proprietary name to the Agency for review prior to its implementation.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of carcinogenicity.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA is not yet sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1719-1 To evaluate the potential for a serious risk of carcinogenicity, conduct a long-term (2 year) rodent carcinogenicity study in the rat. Submit the carcinogenicity protocol for a Special Protocol Assessment prior to initiating the study.

The timetable you submitted on March 2, 2011, states that you will conduct this study according to the following schedule:

Special Protocol Assessment Submission:	December 2011
Final Protocol Submission:	March 2012
Final Report Submission:	December 2014

1719-2 To evaluate the potential for a serious risk of carcinogenicity, conduct a rodent carcinogenicity study in the mouse. Submit the carcinogenicity protocol for a Special Protocol Assessment prior to initiating the study.

The timetable you submitted on March 2, 2011, states that you will conduct this study according to the following schedule:

Special Protocol Assessment Submission:	March 2012
Final Protocol Submission:	June 2012
Final Report Submission:	December 2013

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a known serious risk of vortex keratopathy and corneal stromal changes, to assess signals of excessive toxicity at the studied dose and heart failure, and to identify an unexpected, serious risk of an adverse effect on overall survival.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1719-3 Conduct a randomized dose-finding trial in which patients with progressive or symptomatic medullary thyroid cancer will be randomized to vandetanib 300 mg or 150 mg daily. The trial will include analyses of the safety and activity of the 150 mg dose of vandetanib. Safety assessments will include evaluations of vortex keratopathy and corneal stromal changes, with ophthalmology examination every 6 months with corneal photographs of abnormalities. Safety assessments will also include evaluation of heart failure using serial echocardiograms in all patients. A primary endpoint will include overall response rate.

The timetable you submitted on March 2, 2011, states that you will conduct this trial according to the following timetable:

Final Protocol Submission:	September 2011
Trial Completion Date:	July 2014
Final Report Submission:	December 2014

1719-4 Submit the results of the final analysis of overall survival data from the randomized clinical trial of vandetanib 300 mg vs. placebo in medullary thyroid cancer (Study 58).

The timetable you submitted on March 16, 2011, states that you will conduct this trial according to the following timetable:

Trial Completion Date:	December 2013
Final Report Submission:	May 2014

Submit the protocols to your IND 60042, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify each submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **"Required Postmarketing Protocol Under 505(o)"**
- **"Required Postmarketing Final Report Under 505(o)"**
- **"Required Postmarketing Correspondence Under 505(o)"**

With regard to the carcinogenicity studies (postmarketing requirements 1719-1 and 1719-2), submit the protocols for a Special Protocol Assessment prior to initiating the carcinogenicity study. Notify the Agency in writing at least 30 days prior to submission of the study that a carcinogenicity protocol will be arriving. Submit each carcinogenicity protocol and questions regarding the protocol with sufficient time prior to the anticipated initiation of the study to allow for meaningful discourse with the Agency and resolution of any issues before study initiation. Clearly label the submission with bold black letters as a **REQUEST FOR SPECIAL PROTOCOL ASSESSMENT**. Once the study has been completed, submit the final study report and a prior approval labeling supplement containing proposed labeling to update package inserts to reflect study findings.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o)

on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. The details of the REMS requirements were outlined in our REMS notification letter dated January 21, 2011.

Pursuant to 505-1(f)(1), we have determined that vandetanib can be approved only if elements necessary to assure safe use are required as part of a REMS to mitigate the risks of QT prolongation, Torsades de pointes, and sudden death that are listed in the labeling. The elements to assure safe use will:

- Educate prescribers about the risk, appropriate monitoring, and management of QT prolongation to help minimize the occurrence of Torsades de pointes and sudden death; and
- Inform patients about the serious risks associated with vandetanib.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Your proposed REMS, submitted on April 6, 2011, and appended to this letter, is approved. The REMS consists of a Medication Guide, communication plan, elements to assure safe use, implementation system, and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include, but is not limited to, the following:

a. With regard to the assessment of the Medication Guide:
    i. An evaluation of patients' understanding of the serious risks of vandetanib
    ii. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
    iii. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

b. With regard to the assessment of the communication plan:
    i. The date of product launch and the launch of the communication plan
    ii. The date(s) of mailing(s) and number of recipients of the Dear Healthcare Provider (DHCP) letter and Dear Professional Society Letter
    iii. The number of mailings returned
    iv. The sources of the recipient lists
    v. A copy of all documents included in each mailing

vi. The names and dates of any conferences attended by AstraZeneca and where commercial vandetanib product information was displayed

c. With regard to Prescriber Certification:
   i. The number of healthcare providers accessing the training program (during the reporting period and cumulative)
   ii. The number of healthcare providers who complete the training program but do not complete enrollment (during the reporting period and cumulative)
   iii. The number of healthcare providers enrolled in the vandetanib REMS (during the reporting period and cumulative) and stratified by prescriber specialty
   iv. A summary of the method prescribers used to enroll (online or phone)
   v. Proportion of prescribers that correctly answer each training program question and stratified by specialty
   vi. The number of enrolled healthcare providers actively prescribing vandetanib during the reporting period (i.e., have written at least one prescription in the time period)
   vii. The number of healthcare providers who have ordered/prescribed vandetanib who were not enrolled (during the reporting period and cumulative)

d. With regard to Pharmacy Certification and distributors:
   i. The number of pharmacies enrolled (during the reporting period and cumulative)
   ii. The number of pharmacies ordered/dispensed vandetanib who were not enrolled
   iii. The number of distributors that distributed vandetanib who were not enrolled (during the reporting period and cumulative)

e. With regard to Risk of QT prolongation, Torsades de pointes, and sudden death:
   i. An *analysis* of the post-marketing cases for Torsades de pointes or sudden death reported in association with vandetanib to AstraZeneca (during the reporting period and cumulative) with attention to possible factors that prolonged the QTc (e.g., interacting medication initiated, change in patient's health status, failure to adjust dose, lack of ECG monitoring, lack of electrolyte monitoring, etc.).
   ii. The number of patients who were dispensed vandetanib (during the reporting period and cumulative)
   iii. An evaluation of healthcare providers' understanding of the serious risks of vandetanib

f. Based on the information submitted, an assessment of and conclusion regarding whether the REMS is meeting its goals, and whether modifications to the REMS are needed.

g. Specification of measures that would be taken to increase awareness if surveys of patients or healthcare providers indicate that awareness is not adequate.

h. Assessments of an approved REMS must also include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

Assessments of the vandetanib REMS are required every 6 months for the first year following the approval of the REMS, and annually thereafter. The first assessment should contain all of the above information with the exception of the evaluations of patients' and prescribers' understanding of the serious risks of vandetanib. These evaluations should be included in the second assessment and each annual assessment thereafter.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If you plan to distribute an authorized generic product under this NDA, you must submit a complete proposed REMS that relates only to the authorized generic product. Submit a proposed REMS, REMS supporting document, and any required appended documents as a prior approval supplement. Approval of the proposed REMS is required before you may market your authorized generic product.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 022405 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 022405
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 022405
REMS ASSESSMENT

PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert 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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

CHEMISTRY, MANUFACTURING, AND CONTROLS

Based on the provided stability data, a 36-month expiration dating period is granted for this drug product when stored at 25°C (77°F) excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

METHODS VALIDATION

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

REPORTING REQUIREMENTS

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

MEDWATCH-TO-MANUFACTURER PROGRAM

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 http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Lisa Skarupa, Regulatory Project Manager, at (301) 796-2219.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Office Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration

ENCLOSURE:
- Content of Labeling
- Medication Guide
- Container Labeling
- REMS

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

/s/

RICHARD PAZDUR
04/06/2011