

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

208065Orig1s000

Trade Name: Tagrisso

Generic Name: osimertinib

Sponsor: AstraZeneca Pharmaceuticals, LP

Approval Date: November 13, 2015

Indication: TAGRISSO is indicated for the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC), as detected by an FDA-approved test, who have progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy.

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RESEARCH**

APPLICATION NUMBER:

208065Orig1s000

APPROVAL LETTER



NDA 208065

ACCELERATED APPROVAL

AstraZeneca Pharmaceuticals LP
Attention: Jonathan Jazayeri, Pharm.D., M.S., R.A.C.
Regulatory Affairs Director, Oncology
One MedImmune Way
Gaithersburg, MD 20878

Dear Dr. Jazayeri:

Please refer to your New Drug Application (NDA) dated June 5, 2015, received June 5, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for TAGRISSO (osimertinib), 40 mg and 80 mg tablets.

We acknowledge receipt of your amendments dated June 10, June 16, June 22, June 24, June 26, July 1, July 2 (2), July 10 (2), July 15, July 16, July 17, July 22, July 23, August 5, August 13, August 14, August 17, August 19 (2), September 1, September 2, September 8, September 29, October 8 (3), October 9, October 13 (2), October 20, October 22, November 6, 2015(2), November 10, 2015, November 12, 2015 (4).

This new drug application provides for the use of TAGRISSO (osimertinib), 40 mg and 80 mg tablets for the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive-non-small-cell lung cancer (NSCLC), as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy.

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

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 patient package insert). 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

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).” Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 208065.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

DATING PERIOD

The shelf life for TAGRISSO shall be 12 months from the date of manufacture when stored at USP controlled temperature (20 °C to 25 °C (68 °F to 77 °F)). The start of the shelf life is designated [REDACTED] (b) (4)

The comparability protocol to change the [REDACTED] (b) (4) [REDACTED] is acceptable, but this change must be reported as a CBE-30 and not a CBE-0.

ADVISORY COMMITTEE

Your application was not referred to an FDA advisory committee because the safety profile is acceptable for the approved indication, the clinical trial design is similar to that previously used to support accelerated approval for lung cancer, evaluation of the application did not raise significant safety or efficacy issues in the intended population, and there were no controversial issues that would benefit from an advisory committee discussion.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled clinical trials to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated October 9, 2015. This requirement, along with required completion dates, is listed below.

- 2978-1** Conduct and submit the results of at least one multicenter, randomized clinical trial establishing the superiority of osimertinib over available therapy as determined by progression-free or overall survival in patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC)

The timetable you submitted on October 28, 2015, states that you will conduct this trial according to the following schedule:

| | |
|--------------------------|-----------|
| Trial Completion: | 3/31/2017 |
| Final Report Submission: | 7/31/2017 |

Submit clinical protocols to your IND 117879 for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each requirement in your annual report to this NDA. The status summary should include expected trial completion and final report submission dates, any changes in plans since the last annual report, and, for clinical trials, number of patients entered into each trial.

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated “**Subpart H Postmarketing Requirement(s).**”

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(s) 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 assess signals of a serious risk of toxicity from drug over-exposure due to the effects of impaired hepatic function on the pharmacokinetics of TAGRISSO (osimertinib), and drug-drug interactions of TAGRISSO (osimertinib) with substrates and inhibitors of CYP3A4.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess signals of a serious risk of toxicity from drug over-exposure due to the effects of impaired hepatic function on the pharmacokinetics of TAGRISSO (osimertinib), and drug-drug interactions of TAGRISSO (osimertinib) with substrates and inhibitors of CYP3A4.

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

- 2978-2** Complete a pharmacokinetic trial to determine an appropriate dose of osimertinib in patients with mild to moderate hepatic impairment in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.” found at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072123.pdf>.

The timetable you submitted on October 28, 2015, states that you will conduct this trial according to the following schedule:

Trial Completion: 12/31/2018
Final Report Submission: 5/31/2019

2978-3 Complete a clinical trial to evaluate the effect of a strong CYP3A4 inhibitor on the pharmacokinetics of osimertinib. Conduct this trial in accordance with the FDA draft Guidance for Industry entitled “Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>.

The timetable you submitted on October 28, 2015, states that you will conduct this trial according to the following schedule:

Final Report Submission: 12/31/2015

Submit the protocols to your IND 117879, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the 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).”**

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.

**POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS
UNDER SECTION 506B**

We remind you of your postmarketing commitments:

- 2978-4** Complete a clinical trial to evaluate the effect of a strong CYP3A4 inducer on the pharmacokinetics of osimertinib in accordance with the FDA draft Guidance for Industry entitled “*Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>

The timetable you submitted on October 28, 2015, states that you will conduct this trial according to the following schedule:

Trial Completion: 7/31/2015
Final Report Submission: 12/31/2015

- 2978-5** Complete a clinical trial to evaluate the effect of repeated doses of osimertinib on the pharmacokinetics of a probe substrate of CYP3A4 in accordance with the FDA draft Guidance for Industry entitled “*Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>.

The timetable you submitted on October 28, 2015, states that you will conduct this trial according to the following schedule:

Trial Completion: 4/30/2015
Final Report Submission: 12/31/2015

- 2978-6** Complete a clinical trial to evaluate the effect of repeated doses of osimertinib on the pharmacokinetics of a probe substrate of breast cancer resistant protein (BCRP) in accordance with the FDA draft Guidance for Industry entitled “*Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>.

The timetable you submitted on October 28, 2015, states that you will conduct this trial according to the following schedule:

Trial Completion: 7/31/2015
Final Report Submission: 12/31/2015

PROMOTIONAL MATERIALS

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved package insert (PI)/Medication Guide/patient PI (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

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 the 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 APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval 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.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Ingrid Fan, Regulatory Project Manager, at (301) 796-5053.

Sincerely,

{See appended electronic signature page}

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

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
11/13/2015