CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208065Orig1s000

OFFICE DIRECTOR MEMO

Office Director Summary Review for Regulatory Action

Date	Electronic stamp date
From	Richard Pazdur
Subject	Office Director Summary Review
NDA #	NDA 208065
Applicant Name	AstraZeneca Pharmaceuticals, LP
Date of Submission	June 5, 2015
PDUFA Goal Date	February 5, 2016
Proprietary Name / Established (USAN) Name	Tagrisso/ osimertinib
Dosage Forms / Strength	Tablet for oral administration/ 40 mg and 80 mg tablets
Proposed Indication(s)	"for the treatment of patients with (b) (4) 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. An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials."
Recommended Action for NME:	*Accelerated Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Division Director Review	Patricia Keegan
Regulatory Project Manager Review	Ingrid Fan
Medical Officer/Statistical Review	Sean Khozin, Chana Weinstock, & Joyce Cheng
Pharmacology Toxicology Review	Shawna Weis
CMC Review/OBP Review	Olen Stephens (Technical Lead); William M. Adams (Drug Product); Charles Jewell (Drug Substance); Ying Zhang (Process)
Biopharmaceutics	Gerlie Giesser & Okpo Eradiri
Microbiology & Process Review	Ying Zhang
Facility Review	Thuy Nguyen
Clinical Pharmacology Review	Jun Yang, Ada Zhuang, Ping Zhao, & Rosane Charlab Orbach
OSI	Lauren Iacono-Connors
OSE/DMEPA review	Otto Townsend
OSE/DRISK review	Carolyn L. Yancey
DPMH review	Carol H. Kasten
QT IRT	Huifang Chen
OPDP	Nazia Fatima
Patient Labeling Team Review	Nathan Caulk
CDTL Review	Gideon Blumenthal

OND=Office of New Drugs
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
DPMH=Division of Pediatric and Maternal Health
IRT=Interdisciplinary Review Team
OPDP=Office of Prescription Drug Products
CDTL=Cross-Discipline Team Leader

1. Introduction & Background

On June 5, 2015, AstraZeneca Pharmaceuticals submitted an NDA for Tagrisso (osimertinib) for the treatment of patients with [redacted] (b) (4) 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. Tagrisso (osimertinib) is a kinase inhibitor of both the wild-type and certain mutations of EGFR; osimertinib also inhibits the activity of HER2, HER3, HER4, ACK1, and BLK.

Indicated Population and Available Therapy

Based on SEER, there will be an estimated 221,200 new cases (approximately 85% will be NSCLC) and 158,040 deaths due to lung cancer in the United States in 2015[1]. In the United States, approximately 15% of patients with adenocarcinoma of the lung harbor activating EGFR mutations[2]. Approximately half (57%) of new cases of lung cancer are metastatic at diagnosis; these patients have an estimated 5-year survival rate of 4.2%. While the SEER database does not provide information in genetically defined subgroups of NSCLC (i.e., those with EGFR mutations), the reported median overall survival (OS) times were 22.9 months and 28 months for EGFR TKI-treated patients in randomized trials of erlotinib and afatinib, respectively, which confirms the serious and life-threatening nature of EGFR mutation-positive NSCLC despite the availability of erlotinib, gefitinib, and afatinib.

Drugs which are FDA-approved for the treatment of patients with EGFR mutation-positive (exon 19 deletion or L858R substitution) metastatic NSCLC are erlotinib, afatinib, and gefitinib. There are no drugs which are FDA-approved for the treatment of patients with [redacted] (b) (4) metastatic EGFR T790M mutation-positive-NSCLC, as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy, thus this is an unmet medical need.

FDA-approved drugs for the treatment of patients with NSCLC who have disease progression following platinum-based chemotherapy, [redacted] (b) (4) are listed below with a summary of efficacy results. Based on the low overall response rates (ORR) observed with these drugs, osimertinib appears to provide an advance (based on ORR) over these drugs.

Docetaxel is indicated for the treatment of patients with locally advanced or metastatic NSCLC after failure of prior platinum-based chemotherapy. Approval was based on two randomized, open-label, active-controlled trials demonstrating an improvement in OS as compared to best supportive care [HR 0.56 (95% CI: 0.35, 0.88)], with median survival times of 7.5 months and 4.6 months, respectively; similar survival (5.7 months vs. 5.6 months) was observed for patients receiving docetaxel as compared to either vinorelbine or ifosfamide [HR: 0.82 (0.63, 1.06)]. In both trials, the ORR was relatively low: ORR 5.5% (95% CI: 1.1, 15.1) and ORR 5.7% (95% CI: 2.3, 11.3).

Ramucirumab is indicated, in combination with docetaxel, for the treatment of patients with metastatic NSCLC with disease progression on or after platinum-based chemotherapy. Approval was based on randomized, double-blind, study of ramucirumab plus docetaxel versus placebo plus docetaxel, which demonstrated an improvement in OS [HR 0.86 (95% CI: 0.75, 0.98)] and progression-free survival (PFS) [HR 0.76 (95% CI: 0.68, 0.86)]. The median survival was 10.5 months in patients randomized to ramucirumab plus docetaxel and 9.1 months for patients randomized to placebo plus docetaxel. The ORR was 23% (95% CI: 20, 26) for ramucirumab plus docetaxel.

Pemetrexed is indicated as a single-agent for the treatment of patients with locally advanced or metastatic non-squamous NSCLC after prior chemotherapy. Approval was based on a multi-center, randomized, open label, active-control study comparing pemetrexed to docetaxel in patients with NSCLC after prior chemotherapy which demonstrated a marginally significant improvement in OS [HR 0.78 (95% CI: 0.61, 1.0)]. The ORR were 8.5% (95% CI: 5.2-11.7) for those randomized to pemetrexed and 8.3% (95% CI: 5.1-11.5) for those randomized to docetaxel.

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[1] http://seer.cancer.gov/statfacts/html/lungb.html. Accessed November 10, 2015.

[2] Keedy VL, Temin S, Somerfiled MR, Beasley MB, Johnson DH, McShane LM, et al. American Society of Clinicial Oncology clinical opinion: EGFR mutation testing for patients with advanced NSCLC considering 1st line EGFR TKI therapy. J Clin Oncol. 2011;29: 2121-7.

2. CMC/ Biopharmaceutics

There are no issues that would preclude approval from a CMC perspective. The CMC discipline has provided an overall acceptability of the manufacturing of the drug product and drug substance. The drug product is not sensitive to light (b) (4) Microbial testing is not necessary for this drug substance or drug product as release specifications and will be monitored under stability testing. The proposed dissolution method and acceptance criteria were determined to be acceptable and data were provided in the application to bridge from the clinical trials product to the proposed commercial film-coated tablet formulation. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 12 months when at USP controlled temperature (20 ºC to 25 ºC (68 ºF to 77 ºF)) (b) (4)

3. Nonclinical Pharmacology/Toxicology

There are no outstanding issues that would preclude approval from a nonclinical perspective. The NDA contained non-clinical pharmacology studies, 1-month and 13-week toxicology studies in rats and dogs and safety pharmacology studies. FDA agreed that carcinogenicity studies were not required for the proposed indication.

Nonclinical pharmacology studies supported claims regarding inhibition of EGFR wild-type and EGFR T790M, L858R, exon 19 deletion mutations by osimertinib and of its active metabolites (AZ13575104 and AZ13597550) in *in vitro* studies and in tumor xenograft models, with greater activity against EGFR mutations than EGFR wild-type. In addition, inhibition was also observed against HER2, HER3, HER4, ACK1, and BLK at clinically relevant concentrations.

In 13- week nonclinical toxicology studies in rat and dogs, findings predicted by activity against wild type EGFR were observed in the GI tract (diarrhea, inappetence), skin (ulceration), cornea (corneal atrophy), and lungs (macrophage infiltration) were observed in both species at exposures approximating (rat) or 0.5 times (dog) that observed with the recommended human dose of 80 mg daily. The nonclinical toxicology studies in rats suggested impairment of male fertility based on increased pre-implantation losses in unexposed females that had mated with males at exposures as low as 50% of that achievable with the recommended human dose.

Inhibition of cardiac ion channels, including hERG, was observed, however no effects on electrocardiology were observed in safety pharmacology studies. In safety pharmacology studies, there were equivocal findings of decreased contractility in dogs and guinea pigs.

Osimertinib was non-mutagenic in bacterial and mammalian cell assays and was negative for induction of structural chromosome aberrations in primary human peripheral blood mononuclear cells and the rat micronucleus assay. Therefore, product labeling does not recommend specific handling instructions (e.g., references to OSHA website).

In a GLP-compliant dose range-finding study in pregnant dams, administration of osimertinib on gestation days 2 through 20 resulted in increased post-implantation loss and early embryonic death at exposures 1.5 times that achievable with the recommended human dose. Administration of osimertinib on gestation days 6 through 20 at exposures achievable with the recommended human dose suggested an increase in the rate of fetal malformations (anencephaly and missing lung lobe) and variations as compared to controls.

4. Clinical Pharmacology/Pharmacogenomics

There are no outstanding clinical pharmacology issues that would preclude approval.

The NDA contained the following studies and analyses addressing the clinical pharmacology of osimertinib: absorption, distribution, metabolism, and elimination (ADME) studies; single-dose studies in healthy volunteers; single- and multiple-

dose (AURA Phase 1, AURA extension, and AURA2) studies conducted in patients with NSCLC; a food effect study with a high-fat meal, a study evaluating effects of pH-lowering agents on absorption; exposure-response analyses for efficacy (response rate) and safety; and a population pharmacokinetic (popPK) analysis evaluating for effects on intrinsic and extrinsic factors on osimertinib PK.

The recommended Phase 2 dose (RP2D) was based on the optimal biologic dose (OBD), which maximized clinical efficacy and minimized the incidence of adverse reactions arising from interaction with wild-type EGFR.

Osimertinib is predominantly metabolized via CYP3A, with generation of two pharmacologically active metabolites (AZ7550 and AZ5104), which are present at approximately 10% of the exposure of osimertinib. The median time to peak exposure (Cmax) is 6 hours and the median half-life is 48 hours. There was no evidence of a clinically important effect of a high-fat meal or of pH-lowering agents on the absorption of osimertinib. There is insufficient information to identify a safe and effective dose of osimertinib in patients with severe renal impairment or end-stage-renal disease or in patients with moderate or severe hepatic impairment.

There was no evidence of an exposure-response relationship for ORR. There were increasing risks of rash and diarrhea (all grades and ≥ Grade 3) increasing osimertinib exposure. The relationship between ASZ9291 exposure and occurrence of interstitial lung disease (ILD) or ILD-like events was inconclusive.

There was no evidence of a large change in QTc (i.e., >20 ms) following single dose or multiple doses of osimertinib at the recommended dose, however a pharmacokinetic/pharmacodynamic (PK/PD) analysis suggested a concentration-dependent QTc interval prolongation at 80 mg (median increase of 14ms with 90% CI upper bound of 16ms). Based on the ECGs obtained in AURA2, 29% of patients had a QTc interval of >480 milliseconds (ms) and 0.5% of patients had an increase in QTc of >500ms.

5. Clinical Microbiology

Not applicable.

6. Clinical/Statistical-Efficacy

This NDA relies on the results of two, open-label, fixed dose trials enrolling 411 patients with metastatic NSCLC, evidence of disease progression while receiving a first-line EGFR tyrosine kinase inhibitor and documentation of EGFR T790M mutation-positive NSCLC as detected by the cobas® EGFR mutation test. All patients received osimertinib 80 mg once daily until disease progression or unacceptable toxicity. As agreed-upon with FDA, the primary endpoint was ORR as evaluated by Blinded Independent Central Review (BICR) and the key secondary endpoint was duration of response by BICR.

The data from the two trials were pooled from AURA Extension and AURA2 (see below) to obtain more precise estimations of ORR, which were similar to the results in each trial alone. Patient baseline characteristics were also similar.

The AURA Extension trial was designed as an open-label, non-randomized, non-comparative, multiple cohort trial. All patients received osimertinib at the recommended Phase 2 dose (80 mg once daily).

The AURA2 protocol design was an open-label, non-randomized, non-comparative, multiple parallel cohort study to assess the safety and anti-tumor activity of osimertinib at the recommended Phase 2 dose.

Based on the BIRC determination, the confirmed overall response rate (pooled data) is 59% (95% confidence intervals (CI): 54, 64), with 96% of the 243 responders having ongoing responses ranging from 1.1 to 5.6 months. In order to better characterize duration of response, data were provided for a subgroup of 63 patients with T790M mutation-positive NSCLC, with disease progression on a prior EGFR TKI who received osimertinib at 80 mg daily in an earlier dose-escalation/dose

expansion cohort of the AURA trial. In this subgroup, the BICR-confirmed ORR was 51% (32/63) and the median duration of response was 12.4 months.

The median efficacy results for each study and pooled data are summarized in the table below. Four percent of the patients with response have progressed, with a median duration of follow-up for the AURA Extension trial of 4.2 months and for AURA2 of 4.0 months. For the remaining 96% of the 243 responders, the duration of ongoing responses ranges from 1.1 to 5.6 months.

Efficacy Measure (BICR)	Aura Extension (n=201)	AURA2 (n=210)	Pooled (n=411)
Confirmed Objective Response Rate	57%	61%	59%
(95% CI)	(50, 64)	(54, 68)	(54, 64)
Complete Response	0	1%	0.5%
Partial Response	57%	60%	59%

7. Safety

Size of the database,

The overall safety profile of osimertinib was primarily characterized in 411 patients enrolled in AURA Extension and AURA2 who received osimertinib 80 mg daily, with evaluation of a larger patient experience of 813 patients receiving osimertinib 20 to 240 mg daily for uncommon, serious adverse reactions. The most serious adverse reactions of osimertinib identified across all clinical studies (n=813) were interstitial lung disease, cardiomyopathy, and QTc prolongation. Fatal ILD and fatal cardiomyopathy occurred in approximately 0.5% and 0.2% of patients, respectively. Across the 411 patients enrolled in AURA Extension and AURA2, 333 patients were exposed to osimertinib for at least 6 months, 97 patients were exposed for at least 9 months, and no patient was exposed to osimertinib for 12 months. In AURA Extension and AURA 2 studies (n=411), the most common (>20%) adverse reactions in osimertinib-treated patients were diarrhea (42%), rash (41%), dry skin (31%), and nail toxicity (25%).

8. Advisory Committee Meeting

This new molecular entity (osimertinib) was not referred for review to the Oncologic Drugs Advisory Committee (ODAC) because the safety profile is similar to that of other drugs approved for EGFR-mutation positive NSCLC; the clinical trial design is similar to that used to support previously approved products approved under 21 CFR 314.510 for the treatment of a genetically defined subgroup of NSCLC with disease progression following FDA-approved, genetically targeted therapy; and evaluation of the application did not raise significant safety or efficacy issues in the intended population.

9. Pediatrics

On January 13, 2014, FDA designated cobimetinib as an orphan drug for the treatment of (b) (4) melanoma with BRAF V600 mutation. Therefore, cobimetinib for the approved indication is exempt from the requirements of the Pediatric Research Equity Act (PREA).

10. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Accelerated approval.

- Risk Benefit Assessment
  Metastatic, EGFR mutation-positive NSCLC is a serious and life-threatening disease with a median survival of approximately 2 years in two recently conducted randomized clinical trials. There are no drugs specifically approved

for the treatment of patients who progress during first-line EGFR tyrosine kinase inhibitor (TKI) therapy and drugs approved for second-line treatment of NSCLC, following a platinum-based regimen.

In the pooled analysis of AURA Extension and AURA 2, treatment with osimertinib resulted in an ORR of 59% (95% CI: 54, 64). With a median duration of follow-up for the AURA Extension trial of 4.2 months and for AURA2 of 4.0 months, 4% of responding patients have progressed. For the remaining 96% of the 243 responders, the duration of ongoing responses ranges from 1.1 to 5.6 months. In a subgroup of patients enrolled in the AURA trial, who met the key eligibility criteria for the AURA Extension and AURA 2 trials who also received osimertinib 80 mg daily, the BICR-confirmed ORR was 51% (32/63) and the median duration of response was 12.4 months.

The most serious adverse reactions of osimertinib identified across all clinical studies (n=813) were interstitial lung disease (ILD), cardiomyopathy, and QTc prolongation. Fatal ILD and fatal cardiomyopathy occurred in approximately 0.5% and 0.2% of patients, respectively. Across the 411 patients enrolled in AURA Extension and AURA2, 333 patients were exposed to osimertinib for at least 6 months, 97 patients were exposed for at least 9 months, and no patient was exposed to osimertinib for 12 months. In AURA Extension and AURA 2 studies (n=411), the most common (>20%) adverse reactions in osimertinib-treated patients were diarrhea (42%), rash (41%), dry skin (31%), and nail toxicity (25%).

The risk:benefit profile is favorable in that the durable ORR outweighs both the common and serious risks of osimertinib, which are similar to those already accepted by patients who have received a prior EGFR TKI and for whom there is no satisfactory alternative therapy.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  I agree with the division and DRISK reviewer that a REMS is not required to ensure safe and effective use of osimertinib and that the serious risks of interstitial lung disease/interstitial pneumonitis and QTc prolongation can be mitigated through agreed-upon product labeling.

- Recommendation for other Postmarketing Requirements and Commitments
  See action letter.

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

/s/

TAMY E KIM
11/12/2015

RICHARD PAZDUR
11/12/2015