CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215310Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	215310
PDUFA Goal Date	October 26, 2021
OSE RCM #	2021-293
Reviewer Name(s)	Timothy Bernheimer, PharmD
Team Leader	Carolyn Tieu, PharmD, MPH
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	September 10, 2021
Subject	Evaluation of Need for a REMS
Established Name	mobocertinib
Trade Name	Exkivity
Name of Applicant	Takeda Pharmaceuticals USA, Inc
Formulation	Capsules
Dosing Regimen	160 mg orally once daily

Table of Contents

EXECUTIVE SUMMARY 3

1 Introduction 3

2 Background 3

2.1 Product Information 3

2.2 Regulatory History 4

3 Therapeutic Context and Treatment Options 4

3.1 Description of the Medical Condition 4

3.2 Description of Current Treatment Options 4

4 Benefit Assessment 5

5 Risk Assessment & Safe-Use Conditions 6

5.1 QTc Prolongation and Torsades de Pointes 6

5.2 Interstitial Lung Disease/Pneumonitis 7

5.3 Cardiac Toxicity 7

5.4 Diarrhea 7

5.5 Embryo-Fetal Toxicity 7

6 Expected Postmarket Use 8

7 Risk Management Activities Proposed by the Applicant 8

7.1 Other Proposed Risk Management Activities 8

8 Discussion of Need for a REMS 8

9 Conclusion & Recommendations 10

10 Appendices 10

10.1 Table 1: FDA Approved Treatments for NSCLC 10

10.2 References 12

EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Exkivity (mobocertinib) is necessary to ensure the benefits outweigh its risks. Takeda Pharmaceuticals USA, Inc submitted a New Drug Application (NDA) 215310 for Exkivity with the proposed indication for the treatment of adult patients with locally advanced or metastatic non-small lung cancer (NSCLC) with an epidermal growth factor receptor (EGFR) exon 20 insertion mutation as detected by an FDA-approved test, who have progressed on or after platinum-based chemotherapy.

The serious risks associated with Exkivity include QTc prolongation and Torsades de Pointes (also includes a boxed warning), interstitial lung disease/pneumonitis, cardiac toxicity, diarrhea, and embryo-fetal toxicity. These risks are described in the *Warnings and Precautions* section of the labeling. The Applicant did not submit a proposed REMS or risk management plan with this application.

DRM has determined that a REMS is not needed to ensure the benefits of Exkivity outweigh its risks. Exkivity will likely be prescribed by oncologists who have the training in monitoring, diagnosing, and managing the risks and the adverse events associated with Exkivity. The risks are described and communicated through the boxed warning and *Warnings and Precautions* section of labeling.

1 Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Exkivity (mobocertinib) is necessary to ensure the benefits outweigh its risks. Takeda Pharmaceuticals USA, Inc (the Applicant) submitted a New Drug Application (NDA) 215310 for Exkivity with the proposed indication for the treatment of adult patients with locally advanced or metastatic non-small lung cancer (NSCLC) with an epidermal growth factor receptor (EGFR) exon 20 insertion mutation as detected by an FDA-approved test, who have progressed on or after platinum-based chemotherapy.[1] This application is under review in the Division of Oncology 2 (DO2). The Applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Exkivity (mobocertinib), a new molecular entity,[a] is a kinase inhibitor that selectively inhibits and irreversibly binds to EGFR exon 20 insertion mutations. Exkivity is proposed for the treatment of adult patients with EGFR exon 20 insertion mutation-positive metastatic NSCLC, as detected by an FDA-approved test, who have received prior platinum-based chemotherapy. The proposed dosing of Exkivity is 160 mg (four 40 mg capsules) orally once a day until disease progression or unacceptable adverse events.[b] Exkivity is likely to be administered in both inpatient and outpatient settings. Exkivity is not

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

currently approved in any jurisdiction and the application has received fast track designation by the Agency.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 215310 relevant to this review:

- 12/17/2019: Orphan Drug designation granted
- 04/23/2020: Breakthrough Therapy designation granted
- 06/03/2020: Fast Track designation granted
- 06/14/2021: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference.
- 08/04/2021: A Late Cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that the risk of QTC Prolongation and Torsades de Pointes will require a boxed warning.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Lung cancer is the leading cause of cancer-related deaths in the United States and is estimated to be the cause of more than 25% of all cancer deaths.[2] The 5-year relative survival rate from 2010 to 2016 for patients with NSCLC was 25%.[3,c] Estimated new cases of NSCLC and small cell lung cancer (SCLC) combined are 235,760 with 131,880 deaths in the United States for the year 2021.[3] NSCLC accounts for 85% of all lung cancers,[4] with frequency of EGFR exon 20 insertions being reported between 4 and 10% of all observed EGFR mutations in NSCLC.[5,d] Activating mutations in the EGFR gene occur in 10 to 20% of Caucasian and at least 50% of Asian NSCLC patients.[6]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Treatment options for NSCLC include surgery, radiation, chemotherapy and immunotherapy and selection of treatment typically depends on cancer staging. Chemotherapy most commonly consists of cisplatin or carboplatin plus docetaxel, gemcitabine, paclitaxel, vinorelbine, or pemetrexed.[7]

Drugs that target angiogenesis in NSCLC include bevacizumab and ramucirumab and either of these drugs might be used with other targeted therapies for patients who have certain EGFR gene mutations.

Patients who have lung cancer with certain biomarkers may receive targeted drug treatment. Therapies for NSCLC that target either EGFR or EGFR gene mutations include necitumumab, erlotinib, afatinib,

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

gefitnib, osimertinib, and dacomitinib. Patients with EGFR exon 20 insertion mutations generally have a poor response from therapies that target common EGFR mutations.

Amivantamab-vmjw is a monoclonal antibody infusion that targets the EGFR gene exon 20 insertion mutation and is currently the only drug approved for this type of mutation.[8] There is an unmet need for an oral route option for patients who harbor the exon 20 insertion mutation.

See Table 1 in the Appendices for a comparison of FDA approved NSCLC treatments.

4 Benefit Assessment

The efficacy of Exkivity was evaluated in Study AP32788-15-101 (referred to as study 101), a pivotal, phase 1/2, single-arm, open-label, multicohort study. The primary efficacy analysis included 114 patients with metastatic NSCLC with EGFR Exon 20 insertion mutation who had previously been treated with platinum-based chemotherapy. This population of patients is referred to as the Pooled Prior Platinum Analysis Set. The median age of patients was 60 years (range 27 to 84), with seven percent being ≥ 75 years old. Most (66%) patients were female. Sixty percent of patients were Asian and 37% were White. Patients with a history of interstitial lung disease, drug-related pneumonitis, radiation pneumonitis that required steroid treatment, or significant, uncontrolled, active cardiovascular disease, or prolonged QTc interval were not enrolled in the clinical program.

Patients in the Pooled Prior Platinum Analysis Set were administered 160 mg of Exkivity once daily and disease status was assessed every eight weeks after first dose for 14 cycles, and then every 12 weeks thereafter until end of treatment.

Efficacy was determined by the primary endpoint of objective response rate (ORR) and secondary endpoint of duration of response (DOR), as assessed by the investigator and an independent review committee (IRC) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria for response. Progression assessments were based on standard imaging (CT or MRI scans). IRC assessments were not disclosed to investigators. Per the IRC assessment, the ORR is 28% (95% CI: 20, 37) in the primary analysis population.[e] At the time of the data cut-off, median DOR was 17.5 months (95% CI: 7.4, 20.3). Fifty nine percent of responders had a response that lasted six months or longer and 19% of the responders had a response that lasted 12 months or longer.

The clinical reviewer concludes that Exkivity demonstrated a sufficient and durable ORR in the primary efficacy population and that the observed ORR, along with the observed duration of responses, are clinically meaningful in the context of the poor prognosis of the disease and the limited available approved therapies.

Refer to the FDA NDA Multidisciplinary Review and Evaluation: NDA 215310 Exkivity (mobocertinib) for more information.[9]

[e] Section 505-1 (a) of the FD&C Act: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition

5 Risk Assessment & Safe-Use Conditions

The Mobocertinib 160 mg QD analysis population, which consisted of 256 patients made up the safety database. Patients who received at least one dose of Exkivity at 160 mg from Study 101 and Part 1 of TAK-788-1003 were included in the safety database. Part 1 of TAK-788-1003 was an open-label, multicenter, dose-escalation study in 20 Japanese patients with locally advanced or metastatic NSCLC that were treated with 40 mg to 160 mg of Exkivity everyday orally continuously in 28-day cycles.

Forty-eight percent (48%) of patients were exposed to Exkivity for six months or longer and 12% were exposed for greater than one year.

Serious adverse reactions that led to dose discontinuations or reductions occurred in 46% of patients who received Exkivity. The most common serious adverse reactions were diarrhea (8%), dyspnea (7%), vomiting (4.4%), pyrexia (3.5%), and nausea (2.6%). Fatal adverse reactions occurred in 2.6% of patients who received Exkivity, including cardiac failure (0.9%), dyspnea (0.9%) and pneumonitis (0.9%).

Most treatment discontinuations were due to progressive disease and the most common reason for study discontinuation was death. In the 160 mg QD population there were 27 deaths with 14 (48%) patient deaths due to disease progression. In the clinical review of patient narratives, the fatal AEs which Exkivity's involvement could not be ruled out included three cases of respiratory failure and one case of cardiac failure. Permanent discontinuation of Exkivity occurred in 17% of patients, with diarrhea and nausea adverse reactions being the reason in at least ≥2% of patients.

The *Warnings and Precautions* section of the labeling include risks of QTc Prolongation and Torsades de Pointes, Interstitial Lung Disease/Pneumonitis, Cardiac Toxicity, Diarrhea, and Embryo-Fetal Toxicity. At the time of this review the label was not finalized; however, the draft label will include the risk of QTc Prolongation and Torsades de Pointes as a boxed warning.[f]

5.1 QTc Prolongation and Torsades de Pointes

In the pooled Exkivity safety population, 250 patients had scheduled and unscheduled electrocardiograms (ECGs). QTc interval > 500 msec was detected in 3 (1.2%) patients and 27 (11%) patients had a change-from-baseline QTc interval >60 msec. Torsades de Pointes occurred in 1 patient (0.4%). Patients with a baseline QTc greater than 470 msec were not enrolled in the Exkivity clinical program. There were no deaths reported due to QTc prolongation or Torsades de Pointes in the pooled Exkivity safety population.

The review team recommends a boxed warning for the life-threatening and fatal risk of QTc prolongation and Torsades de Pointes to inform healthcare professionals of this serious risk. The label advises healthcare providers to assess QTc and electrolytes at baseline prior to initiation of Exkivity and to continue monitoring during treatment. Increased frequency of monitoring is advised in patients with risk factors for QTc prolongation and drugs known to prolong the QTc interval should be avoided. Based

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

on the severity of the QTc prolongation, doses of Exkivity may need to be reduced, withheld, or permanently discontinued.

5.2 INTERSTITIAL LUNG DISEASE/PNEUMONITIS

Interstitial lung disease/pneumonitis, which can be fatal, was detected in the pooled Exkivity safety population. Interstitial lung disease/pneumonitis occurred in 4.3% of patients including 0.8% Grade 3 events and 1.2% fatal events.

The label advises healthcare providers to monitor patients for new or worsening pulmonary symptoms and to immediately withhold Exkivity in patients with suspected interstitial lung disease/pneumonitis.

5.3 CARDIAC TOXICITY

Cardiac toxicity was reported in the pooled Exkivity safety population. In the pooled safety population cardiac failure occurred in 2.7% of patients including 1.2% Grade 3 reactions, 0.4% Grade 4 reactions, and one (0.4%) fatal case of cardiac failure.

Atrial fibrillation (1.6%), ventricular tachycardia (0.4%), first degree atrioventricular block (0.4%), second degree atrioventricular block (0.4%), left bundle branch block (0.4%), supraventricular extrasystoles (0.9%) and ventricular extrasystoles (0.4%) also occurred in patients receiving Exkivity.

The label advises healthcare providers to monitor cardiac function, including assessment of left ventricular ejection fraction at baseline and during treatment and to permanently discontinue Exkivity (b) (4)

5.4 DIARRHEA

Diarrhea, which can be severe, occurred in 93% of patients including 20% Grade 3 and 0.4% Grade 4. First onset of diarrhea has occurred 24 hours after the administration of Exkivity with the median time observed in the population as five days after administration.

The label advises healthcare providers to monitor electrolytes and withhold, reduce the dose or permanently discontinue Exkivity based on the severity of diarrhea and to treat promptly because prolonged diarrhea may lead to dehydration or electrolyte imbalance, with or without renal impairment. Patients are advised to start an anti-diarrheal agent immediately after the first sign of diarrhea or increased bowel movement frequency and to increase fluid intake.

5.5 EMBRYO-FETAL TOXICITY

Based on Exkivity's mechanism of action and on findings from animal studies, it is believed that embryo-fetal toxicity can occur when Exkivity is administered during pregnancy. Embryolethality was observed at maternal exposures approximately 1.7 times human exposures when administered to rats during the period of organogenesis.

The label advises females of reproductive potential to use effective non-hormonal contraception during treatment with Exkivity and for one month after the last dose because Exkivity may render hormonal contraceptives ineffective. Males with female partners of reproductive potential are advised to use effective contraception during treatment with Exkivity and for one week after last dose.

6 Expected Postmarket Use

Lung cancer is the leading cause of cancer related death in the United States and Exkivity's use will be in a subset of adult lung cancer patients with EGFR exon 20 insertion mutation-positive metastatic NSCLC, as detected by an FDA-approved test, who have received prior platinum-based chemotherapy. Exkivity will be used in oncology settings where lung cancer patients are treated, both inpatient and outpatient. The risks of Exkivity are similar to other kinase inhibitors specific to EGFR (see Table 1 in the Appendix). Similar to amivantamab-vmjw, the only other currently approved EGFR exon 20 insertion specific medication, the risks associated with Exkivity include: interstitial lung disease/pneumonitis, diarrhea, and embryo-fetal toxicity. In addition, the risk of QTc prolongation and Torsades de Pointes will be communicated in a box warning. Likely prescribers of Exkivity will be oncologists who should be familiar with the management of the risks of Exkivity treatment, including the expertise to identify new or worsening pulmonary symptoms and who understand the importance of monitoring for QTc prolongation and cardiac toxicities.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for Exkivity beyond routine pharmacovigilance and labeling.

7.1 Other Proposed Risk Management Activities

The review team has determined that the following post marketing requirements (PMRs) relevant to the serious safety concerns mentioned in this review are necessary for the Applicant to complete:

1. Conduct an integrated safety analysis containing data from randomized clinical trials to further characterize the known serious signal of QT prolongation, ventricular arrhythmia and Torsades de Pointes.

Reviewer's Comments: *We note that the PMRs proposed by the review team are outside of the scope of the REMS program and defer to Division of Epidemiology for review and input.*

8 Discussion of Need for a REMS

The clinical review team recommends approval of Exkivity based on the efficacy and safety information currently available for the treatment of adult patients with locally advanced or metastatic NSCLC with an EGFR exon 20 insertion mutation as detected by an FDA-approved test, who have progressed on or after platinum-based chemotherapy

In the United States, lung cancer is the most common form of cancer and patients with NSCLC are estimated to have a 5-year relative survival rate of 25%. Treatment of NSCLC requires a multifaceted approach which includes chemotherapy, medications that inhibit angiogenesis, and targeted treatment for patients that have cancer that contain certain biomarkers. Currently there is only one FDA-approved product (Amivantamab-vmjw, which requires an infusion) that targets the EGFR exon 20 insertion

mutation. There are currently no oral formulation products that target EGFR exon 20 insertion mutations. As a result, there is an unmet need for additional EGFR exon 20 insertion target products that are not restricted to certain treatment settings.

The review team concludes that the benefits for patients with EGFR exon 20 insertion mutation-positive metastatic NSCLC, who have received prior platinum-based chemotherapy, outweigh potential risks associated with Exkivity. The risks of QTc prolongation and Torsades de Pointes, interstitial lung disease/pneumonitis, cardiac toxicity, diarrhea, and embryo-fetal toxicity, will be described in the *Warnings and Precautions* section of the label. Additionally, there will be a boxed warning for the risk of QTc prolongation and Torsades de Pointes. This reviewer agrees with the clinical reviewer's conclusion that these adverse events can be communicated through labeling and are manageable with dose reduction, dose withholding, or dose discontinuation.

Other FDA approved treatments for NSCLC also share the risks of QTc prolongation (osimertinib), interstitial lung disease/pneumonitis (erlotinib, afatinib, gefitnib, osimertinib, dacomitinib, and amivantamab-vmjw), cardiac toxicity (bevacizumab), diarrhea (afatinib, gefitnib, and dacomitinib), and embryo-fetal toxicity (all). None of these products are approved with a REMS and risks are described and communicated through a boxed warning and/or warnings and precautions in labeling.

Osimertinib (approved in 2015) has the risk of QTc Prolongation described in the *Warnings and Precaution* section of labeling and does not have a boxed warning. In the osimertinib safety population, QTc interval > 500 msec was detected in 1 (0.2%) patient and 11 (2.7%) patients had a change-from-baseline QTc interval >60 msec[10] compared to 3 (1.2%) and 27 (11%) patients, respectively, having change-from-baseline detected in the safety population for Exkivity (See Table 1 in the Appendices).

Caprelsa is also a kinase inhibitor, indicated for the treatment of symptomatic or progressive medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease. Caprelsa was approved in 2011 with a REMS to mitigate the serious risks of QTc prolongation, Torsades de pointes, and sudden death associated with use. In the Caprelsa safety database, more than 35% of patients experienced > 60 ms increase in QTc (versus 11% in the Exkivity safety database), there were 11 cases of sudden death, and two documented cases of Torsades de pointes.[11] There were zero cases of sudden death and one case of Torsades de pointes in the Exkivity safety data. Caprelsa has a much longer half-life than Exkivity (19 days verses 18 hours, respectively), therefore reducing the dose or discontinuing Caprelsa will not produce a quick reduction in risk. The benefits and risks for Caprelsa and the need for a REMS are also impacted by the actual or intended duration of treatment and seriousness of the condition being treated. MTC is a disease that progresses over many years, and therefore patients may have many years of drug exposure. The benefit/risk for Caprelsa with regard to disease progression and the seriousness of the risk of QTc prolongation resulting in sudden death are different than they are for Exkivity.

Exkivity will likely be prescribed by oncologists who have the training in monitoring, diagnosing, and managing the risks and the adverse events associated with Exkivity.

This reviewer has determined that a REMS is not necessary to ensure the benefits of Exkivity outweigh its risks. Likely prescribers are expected to understand the importance of monitoring for the risks of Exkivity described and communicated through the boxed warning and *Warnings and Precautions* section of the labeling.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for Exkivity to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 TABLE 1: FDA APPROVED TREATMENTS FOR NSCLC

Product Trade Name (Generic) **Year of Approval**	**Indication**	**Dosing and Administration**	**Risk Management Approaches/Boxed Warning, Medication Guide**
Angiogenesis Inhibitors			
Avastin (bevacizumab)[12] 2006	Unresectable, locally advanced, recurrent, or metastatic non-squamous NSCLC, in combination with carboplatin and paclitaxel for first-line treatment	15 mg/kg every 3 weeks with carboplatin and paclitaxel	**Warnings and Precautions:** Gastrointestinal Perforations and Fistula, Surgery and Wound Healing Complications, Hemorrhage, Arterial Thromboembolic Events (ATEs), Venous Thromboembolic Events (VTEs), Hypertension, Posterior Reversible Encephalopathy Syndrome, Renal Injury and Proteinuria, Infusion-Related Reactions (IRR), Embryo-Fetal Toxicity, Ovarian Failure, Congestive Heart Failure
Cyramza[13] (ramucirumab) 2014	In combination with erlotinib, for first-line treatment of metastatic NSCLC with EGFR exon 19 deletions or exon 21 (L858R) mutations	Infusion, 10 mg/kg every 2 weeks with daily erlotinib or 10 mg/kg on Day 1 of a 21-day cycle prior to docetaxel.	**Warnings and Precautions:** ATEs, Hypertension, IRR, Worsening of Pre-existing Hepatic Impairment, Posterior Reversible Encephalopathy Syndrome, Proteinuria Including Nephrotic Syndrome, Thyroid Dysfunction, Embryo Fetal Toxicity

EGFR Inhibitors and EGFR Mutation Targeted Therapies			
Portrazza (necitumumab)[14] 2015	In combination with gemcitabine and cisplatin, for first-line treatment of patients with metastatic squamous NSCLC. Limitation of Use: not indicated for treatment of non-squamous NSCLC	800 mg (absolute dose) as an intravenous infusion over 60 minutes on Days 1 and 8 of each 3-week cycle.	**Boxed warning:** Cardiopulmonary Arrest and/or sudden death, Hypomagnesemia **Warning and Precautions:** VTE and ATE, Dermatologic Toxicities, IRR, Increased Toxicity, Embryo-Fetal Toxicity
Tarceva (erlotinib)[15] 2004	Treatment of patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test receiving first-line, maintenance, or second or greater line treatment after progression following at least one prior chemotherapy regimen. Limitations of Use: Safety not established in patients whose tumors have other EGFR mutations. Not recommended for use in combination with platinum-based chemotherapy.	150 mg orally, on an empty stomach, once daily	**Warning and Precautions:** Interstitial lung disease (ILD), Renal failure, Hepatotoxicity, Gastrointestinal perforations, Bullous and exfoliative skin disorders, Cerebrovascular accident (CVA), Microangiopathic hemolytic anemia (MAHA), Ocular disorders, Hemorrhage in patients taking warfarin, Embryo-fetal toxicity
Gilotrif (afatinib)[16] 2013	For the first-line treatment of patients with metastatic NSCLC) whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test Limitations of Use: Safety and efficacy not established in patients whose tumors have resistant EGFR mutations	40 mg orally once daily	**Warnings and Precautions:** Diarrhea, Bullous and exfoliative skin disorders, ILD, Hepatic toxicity, Gastrointestinal perforation, Keratitis, Embryo-fetal toxicity
Iressa (gefitnib)[17] 2003/2015	For the first-line treatment of patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.	250 mg orally, once daily with or without food	**Warnings and Precautions:** ILD, Hepatotoxicity, Gastrointestinal perforation, Diarrhea, Ocular Disorders including Keratitis, Bullous and Exfoliative Skin Disorders, Embryo-fetal Toxicity
Tagrisso (Osimertinib)[10]	Adjuvant therapy after tumor resection and or first-line treatment in adult patients with NSCLC whose tumors have EGFR exon 19 deletions or exon 21	80 mg orally once daily, with or without food	**Warnings and Precautions:** ILD/Pneumonitis, QTc Interval Prolongation, Cardiomyopathy, Keratitis, Erythema Multiforme and

2015	L858R mutations, as detected by an FDA-approved test and for the treatment of adult patients with metastatic EGFR T790M mutation positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR TKI therapy.		Stevens-Johnson Syndrome, Cutaneous Vasculitis, Embryo-Fetal Toxicity
Vizimpro (dacomitinib)[18] 2018	For the first-line treatment of patients with metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutations as detected by an FDA-approved test.	45 mg orally once daily with or without food	**Warnings and Precautions:** ILD, Diarrhea, Dermatological Adverse Reactions, Embryo-Fetal Toxicity
EGFR Inhibitors for Exon 20 Insertion Mutations			
Rybrevant (amivantamab-vmjw)[19] 2021	For the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.	1050 mg (body weight less than 80 kg) or 1400 mg (greater than 80 kg) as intravenous infusion weekly for 4 weeks, with the initial dose as a split infusion in Week 1 on Day 1 and Day 2, then administer every 2 weeks thereafter.	**Warnings and Precautions:** IRR, ILD/Pneumonitis, Dermatologic Adverse Reactions, Ocular Toxicity, Embryo-Fetal Toxicity

10.2 REFERENCES

[1] Takeda Pharmaceuticals USA, Inc. Proposed Prescribing Information for Exkivity, July 27, 2021

[2] Lu T, Yang X, Huang Y, et al. Trends in the incidence, treatment, and survival of patients with lung cancer in the last four decades. *Cancer Manag Res*. 2019;11:943-953. doi:10.2147/CMAR.S187317

[3] American Cancer Society: Cancer Facts and Figures 2021. American Cancer Society, 2021. Available online at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2021/cancer-facts-and-figures-2021.pdf. Accessed June 17, 2021.

[4] Duma N, Santana-Davila R, Molina JR. Non-Small Cell Lung Cancer: Epidemiology, Screening, Diagnosis, and Treatment. *Mayo Clin Proc*. 2019;94(8):1623-1640. doi:10.1016/j.mayocp.2019.01.013

[5] Vyse S, Huang PH. Targeting *EGFR* exon 20 insertion mutations in non-small cell lung cancer. *Signal Transduct Target Ther*. 2019;4:5. Published 2019 Mar 8. doi:10.1038/s41392-019-0038-9

[6] Harrison PT, Vyse S, Huang PH. Rare epidermal growth factor receptor (EGFR) mutations in non-small cell lung cancer. Semin Cancer Biol. 2020;61:167-179. doi:10.1016/j.semcancer.2019.09.015

[7] Non-Small Cell Lung Cancer Treatment. Lungcancer.org website. Updated 2021. Accessed July 15, 2021. https://www.lungcancer.org/find_information/publications/163-lung_cancer_101/269-non_small_cell_lung_cancer_treatment. Accessed July 15, 2021.

[8] Treating Non-Small Cell Lung Cancer. American Cancer Society website. Updated June 1, 2021. https://www.cancer.org/cancer/lung-cancer/treating-non-small-cell/targeted-therapies.html. Accessed July 15, 2021.

[9] FDA NDA Multidisciplinary Review and Evaluation: NDA 215310 Exkivity (mobocertinib)) capsules, for oral use. Review in progress; accessed July 27, 2021.

[10] Tagrisso (osimertinib) injection Prescribing Information. AstraZeneca Pharmaceuticals LP. Wilmington, DE 19850. Revised July 2021; https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/208065s022lbl.pdf. Accessed July 27, 2021.

[11] Caprelsa (vandetanib) tablets Prescribing Information. Genzyme Corporation. Cambridge, MA 02142. Revised June 2020; https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022405s017lbl.pdf. Accessed September 9, 2021.

[12] Avastin (bevacizumab) injection Prescribing Information. Genetech, Inc. San Francisco, CA 94080. Revised May 2020; https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125085s337lbl.pdf. Accessed July 27, 2021.

[13] Cyramza (ramucirumab) injection Prescribing Information. Eli Lilly and Company. Indianapolis, IN 46285. Revised June 2021; https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125477s039lbl.pdf. Accessed July 27, 2021.

[14] Portrazza (necitumumab) injection Prescribing Information. Genetech, Inc. Eli Lilly and Company. Indianapolis, IN 46285. Revised November 2015; https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125547s000lbl.pdf. Accessed July 27, 2021.

[15] Tarceva (erlotinib) tablets Prescribing Information. OSI Pharmaceuticals, LLC. Northbrook, IL 60062. Revised October 2016; https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021743s025lbl.pdf. Accessed July 27, 2021.

[16] Gilotrif (afatinib) tablets Prescribing Information. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT 06877. Revised October 2019; https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/201292s015lbl.pdf. Accessed July 27, 2021.

[17] Iressa (gefitinib) tablets Prescribing Information. AstraZeneca Pharmaceuticals LP. Wilmington, DE 19850. Revised May 2021; https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/206995s004lbl.pdf. Accessed July 27, 2021.

[18] Vizimpro (dacomitinib) tablets Prescribing Information. Pfizer, Inc. New York, NY 10017. Revised December 2020; https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/211288s003lbl.pdf. Accessed July 27, 2021.

[19] Rybrevant (amivantamb-vmjw) injection Prescribing Information. Janssen Biotech, Inc. Horsham, PA 19044. Revised May 2021; https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761210s000lbl.pdf. Accessed July 27, 2021.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TIMOTHY J BERNHEIMER
09/10/2021 05:01:08 PM

CAROLYN N TIEU
09/10/2021 05:12:32 PM

CYNTHIA L LACIVITA
09/10/2021 05:32:09 PM