CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211288Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
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	211288
PDUFA Goal Date	September 28, 2018
OSE RCM #	2018-250
Reviewer Name(s)	Naomi Redd, Pharm.D.
Team Leader	Elizabeth Everhart, RN, MSN, ACNP
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	July 3, 2018
Subject	Evaluation of the Need for a REMS
Established Name	Dacomitinib
Trade Name	Vizimpro
Name of Applicant	Pfizer Inc
Therapeutic class	Kinase Inhibitor
Formulation	15mg, 30mg and 45mg tablets
Dosing Regimen	45mg orally once daily until disease progression or unacceptable toxicity

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Vizimpro (dacomitinib) is necessary to ensure the benefits outweigh its risks. Pfizer Inc., submitted a New Drug Application (NDA 211288 for dacomitinib with the proposed indication for the treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) (b) (4) mutations as detected by an FDA-approved test. The risks associated with dacomitinib include interstitial lung disease (ILD)/pneumonitis, diarrhea, dermatologic adverse events, and embryo-fetal toxicity. The applicant did not submit a proposed REMS or risk management plan with this application.

Efficacy was demonstrated by a statistically significant improvement of progression free survival (PFS) in the Applicant's registrational trial, and if approved, dacomitinib will provide another oral based treatment options for the treatment of patients with NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutations. ILD/pneumonitis, diarrhea, dermatologic adverse events, and embryo-fetal toxicity are not new, or unusual events with other EGFR-TKI based therapy for the treatment of NSCLC. Dacomitinib will likely be prescribed by oncologists who are familiar with the safety profile and the management of adverse events associated with EGFR-TKI based therapy.

The proposed label does not include a Boxed Warning, and the risks associated with dacomitinib will be included under Warnings and Precautions in the label. DRISK and the Division of Oncology Products 2 (DOP 2) agree that a REMS is not needed to ensure the benefits of dacomitinib outweigh its risks.

1 Introduction

This review by the DRISK evaluates whether a REMS for the NME Vizimpro (dacomitinib) is necessary to ensure the benefits outweigh its risks. Pfizer Inc., submitted a NDA 211288 for dacomitinib with the proposed indication for the treatment of patients with (b) (4) metastatic NSCLC with EGFR-(b) (4) mutations as detected by an FDA-approved test. The risks associated with dacomitinib include ILD, diarrhea, dermatologic adverse events, and embryo-fetal toxicity. The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Dacomitinib is a pan-human kinase inhibitor with clinical activity against mutated EGFR deletions in exon 19 or the L858R substitution in exon 21. Dacomitinib binds selectively and irreversibly to the human epidermal growth factor (HER) family targets in EGFR/HER1, HER2 and HER4 domains providing prolonged inhibition and antitumor efficacy.[1] The proposed indication is for the first-line treatment of patients with metastatic NSCL with EGFR exon 19 deletion or exon 21 L858R substitution mutations as detected by an FDA-approved test. Dacomitinib is available as 15mg, 30mg, and 45mg tablets. The proposed dose is 45mg taken orally once daily until disease progression or unacceptable toxicity occurs.[a]

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

Dacomitinib is likely to be prescribed by oncologists to patients in an outpatient setting, and this drug is not part of a drug class that has a REMS or a Boxed Warning for the treatment of NSCLC.

Dacomitinib is an NME[b] and was granted Orphan Drug Designation on March 3, 2015 and under Priority Review. Dacomitinib is currently not approved in any other jurisdictions.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 211288 relevant to this review:

- 03/03/2015: Orphan Drug Designation granted
- 01/31/2018: NDA 211288 submission received
- 05/10/2018: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for dacomitinib

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Lung cancer is the leading cause of cancer-related deaths among men and women globally. The According to the American Cancer Society, the estimates for new cases of lung cancer in the United States are approximately 234,030, while approximately 154,050 deaths are expected to occur from this disease.[2] Non-small cell lung cancer (NSCLC) represents approximately 85% of all lung cancer, and the majority of patients present with locally advanced or metastatic disease. Survival rates are dismal when patients present at this stage.[c,d] EGFR-activating mutations occur in 10% to 20% of White patients and in 30% to 50% in East Asian patients with NSCLC out of approximately 1.6 million patients worldwide who are diagnosed with NSCLC each year. These mutations are more common in tumors of non-squamous histology, Asians, women, and people who have no smoking history.[3]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

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

[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.*

Developments in molecular testing techniques and targeted therapies have changed the diagnosis and treatment paradigms for patients with NSCLC. Approximately 69% of patients with advanced NSCLC have been found to have an actionable molecular target.[3,4] Mutations in the adenosine triphosphate (ATP) cleft within the epidermal growth factor receptor (EGFR) tyrosine kinase domain has been found in approximately 20% of NSCLC adenocarcinomas.[4] Patients who have lung neoplasms with specific genomic aberrations in this genome have benefited from molecular targeted therapies.

Gefitinib, erlotinib, osimertinib and afatinib are EGFR tyrosine kinase inhibitors (TKI) used in the treatment for patients with NSCLC. The safety profile of these medications are similar, with varying efficacy rates. None of these medications have been approved with a REMS or have Boxed Warnings. Please see the Appendix for a summary of the safety and labeling profile of these medications.

Despite therapeutic advances in this disease, patients with NSCLC who have EGFR-activating mutations continue to have disease progression within a period of 8 to 11 months after first-line EGFR TKI therapy.[3,4]

4 Benefit Assessment

The efficacy of dacomitinib was demonstrated in a randomized, multicenter, multinational, open-label study (ARCHER 1050; [NCT01774721]). Patients were required to have unresectable, metastatic NSCLC with no prior therapy for metastatic disease or recurrent disease with a minimum of 12-months disease-free after completion of systemic therapy; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; EGFR exon 19 deletion or exon 21 L858R substitution mutations.[1] Patients were randomized (1:1) to receive dacomitinib 45 mg orally once daily or gefitinib 250 mg orally once daily until disease progression or unacceptable toxicity. A total of 452 patients were randomized to receive dacomitinib (n=227) or gefitinib (n=225). The demographic characteristics were 60% female; median age 62 years (range: 28 to 87), with 41% aged 65 years and older; and 23% White, 77% Asian, and less than 1% Black. Prognostic and tumor characteristics were ECOG performance status 0 (30%) or 1 (70%); 59% with exon 19 deletion and 41% with exon 21 L858R substitution; Stage IIIB (8%) and Stage IV (92%); 64% were never smokers; and 1% received prior adjuvant or neoadjuvant therapy.

In this clinical trial, dacomitinib demonstrated a statistically significant improvement in progression free survival (PFS) as determined by a blinded Independent Radiology Central (IRC) review. Efficacy outcome measures are noted in the table below.

Table 1: Efficacy results in ARCHER 1050[1]

	Dacomitinib (n = 227)	Gefitinib (n = 225)

Progression-Free Survival (PFS) Number of patients with event, n (%) Median PFS in months (95% CI)	 136 (59.9) 14.7 (11.1, 16.6)	 179 (79.6) 9.2 (9.1, 11.0)
HR (95% CI)	0.589 (0.469, 0.739)	
p-value	<0.0001	
Overall Survival (OS) Number of patients with event, n (%) Median OS in months (95% CI)	 103 (45.4) 34.1 (29.5, 37.7)	 117 (52.0) 26.8 (23.7, 32.1)
HR (95% CI)	0.760 (0.582, 0.993)	
Objective Response Rate (ORR) ORR % (95% CI)	 75% (68.7, 80.4)	 72.1% (65.2, 77.4)
Duration of Response (DoR) Median DoR in months (95% CI)	 14.8 (12.0, 17.4)	 8.3 (7.4, 9.2)

CI = confidence interval; HR = hazard ratio

The clinical team determined that the results of this study are statistically significant and clinically meaningful, and thus support the approval of dacomitinib.[5,e]

5 Risk Assessment & Safe-Use Conditions

The data described below reflect exposure to dacomitinib in a total of 394 patients; 227 patients in the registrational trial (ARCHER 1050), Study A7471009 (n=38), Study A7471011 (n=83), and Study A7471028 (n=16)] and one single arm trial [Study A7471017 (n=30)]. Patients were excluded if they had a history of interstitial lung disease, interstitial pneumonitis, or brain metastases. The median duration of exposure to dacomitinib was 15.3 months (range 0.7-37.4) Adverse reactions noted in these trials for dacomitinib reported in at least 20% of patients include: rash (90%), diarrhea (87%), stomatitis (72%), nail disorders (66%), decreased appetite (31%), dry skin (34%), decreased weight (26%), conjunctivitis (24%), alopecia (23%), and rhinorrhea (12%).[1] The clinical team notes that the adverse events associated with dacomitinib are dose-dependent, and was reduced by dose adjustments in the majority of reported cases.[5] Currently, there is not a Boxed Warning, and the clinical review team has decided to highlight Interstitial Lung Disease (ILD), diarrhea, dermatologic adverse reactions and embryo-fetal toxicity (based on nonclinical data) in the Warnings and Precautions section. [1, f]

5.1 INTERSTITIAL LUNG DISEASE (ILD)

Severe and fatal ILD/pneumonitis occurred in patients treated with dacomitinib. ILD/pneumonitis occurred in 2% of the 394 dacomitinib treated patients, and 0.3% of these cases were fatal.

[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.*

[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.*

Recommendations are to monitor patients for pulmonary symptoms indicative of ILD/pneumonitis, and to withhold dacomitinib in patients who present with worsening respiratory symptoms ad permanently discontinue if ILD/pneumonitis is confirmed.

5.2 DIARRHEA

Diarrhea occurred in 86% of the 394 dacomitinib patients, and Grade 3 or 4 diarrhea was reported in 11% of patients. Fatality was reported in 0.3% of cases. Recommendations are to withhold dacomitinib until recovery to Grade 1, then resume at the same or reduced dose depending on the severity of diarrhea.

5.3 DERMATOLOGIC EVENTS

Rash, erythematous and exfoliative skin conditions occurred in patients treated with dacomitinib. Rash occurred in 84% of the 394 dacomitinib treated patients, and of these 23% were Grade 3 or 4. Any grade of exfoliative skin conditions were reported in 3.5% of patients, of which there were no grade 3 or 4 events. There were no fatalities due to rash or exfoliative skin conditions. Recommendations are to advise patients to use protective clothing and sunscreen before exposure to the sun, and to withhold dacomitinib until recovery to Grade 1. Resume dacomitinib at the same or reduced dose depending on the severity of the dermatologic event.

5.4 EMBRYO-FETAL TOXICITY

Based on findings from animal studies and its mechanism of action, dacomitinib can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, oral administration of dacomitinib to pregnant rats during the period of organogenesis resulted in an increased incidence of post-implantation loss and reduced fetal body weight at doses resulting in exposures near the exposure at the 45 mg human dose. In the Applicant's registrational trial, 60% were female; median age 62 years (range: 28 to 87), with 41% aged 65 years and older. There were no fetal-toxic events reported. Recommendations are to advise pregnant women of the potential risk to the fetus, and to advise people of reproductive potential to use effective contraception during treatment with dacomitinib, and for at least 17 days after the final dose.

The clinical team notes that while dacomitinib at the proposed starting dose had more toxicity in the clinical trial than gefitinib, it was tolerable for a longer treatment duration for most patients with dose modifications. Based on results from the clinical trial and evidence of safety information in the face of dose modifications and dose reductions, the risk benefit profile of dacomitinib is acceptable and a REMS is not necessary for the approval of dacomitinib to ensure the benefits outweigh the risks.[5]

6 Expected Postmarket Use

Dacomitinib will likely be prescribed by oncologists who are familiar with the adverse events associated with treatment and the management of ambulatory outpatient-patients diagnosed with NSCLC

confirmed by an FDA approved test, specifically for patients with the EGFR exon 19 deletion or exon 21 L858R substitution mutations.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for dacomitinib beyond routine pharmacovigilance and labeling. The Applicant does not propose a Boxed Warning in the labeling. They do propose a "patient information" document.

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of dacomitinib based on the efficacy and safety information currently available.

When evaluating the need for a REMS, DRISK considers factors from Section 505-1 (a) of the Food Drug & Cosmetic Act (i.e., FDAAA factors) to assess the benefit: risk profile for all NME's. These factors include the estimated size of the population, seriousness of disease, the expected benefit, the expected duration of treatment, and the serious of known or potential adverse events. The following is an assessment of these factors as it relates to dacomitinib.

Estimated size of the population and seriousness of disease: Non-small cell lung cancer (NSCLC) represents approximately 85% of all lung cancer, and most patients present with locally advanced or metastatic disease. Survival rates are dismal when patients present at this stage. The American Cancer Society estimates that there will be 234,030 new cases of lung cancer in the United States; 154,050 deaths are expected to occur from this disease. While there have been several advancements in the molecular treatments and targeted-therapy of NSCLC, patients continue to have disease progression within a period of 8 to 11 months after first-line EGFR TKI therapy. There remains a need for therapy to achieve a longer PFS this patient population.

Expected benefit: In the Applicant's registrational trial, dacomitinib demonstrated a statistically significant improvement in progression free survival (PFS) as determined by a blinded Independent Radiology Central (IRC) review. The median time of PFS was nearly 15 months in the dacomitinib arm compared to 9 months in the gefitinib arm.

Duration of treatment: The proposed dose for dacomitinib is 45 mg taken orally once daily until disease progression or unacceptable toxicity occurs. In the Applicant's registrational trial, the median duration of response for dacomitinib was 14 months versus 8 months in the gefitinib arm.

Seriousness of known or potential adverse events: Adverse reactions noted in for dacomitinib reported in at least 20% of patients include: rash, diarrhea, stomatitis, nail disorders, decreased appetite, dry skin, weight loss, conjunctivitis, alopecia, and rhinorrhea. Fatalities from ILD/pneumonitis and diarrhea were reported in a small set of patients. Embryo-fetal toxicity is based on nonclinical information. These adverse events, including the fatal cases from ILD/pneumonitis and diarrhea are adverse events that

have been seen in other EGFR-TKI based therapy for the treatment of NSCLC. If approved, the clinical review team has decided to highlight ILD, diarrhea, dermatologic adverse reactions and embryo-fetal toxicity in the Warnings and Precautions section. The dacomitinib label will not include a Boxed Warning. The clinical team notes that while dacomitinib at the proposed starting dose was associated with more toxicity in the clinical trial than gefitinib, it was tolerable for a longer treatment duration (median duration of treatment in the clinical trial was 14 months versus 8 months for gefitinib) for most patients with dose modifications.

The adverse event profile for dacomitinib is similar to other EGFR TKI agents approved for the treatment of NSCLC. None of the currently approved medications that are like dacomitinib are approved with a REMS or Boxed Warnings. A statistically significant improvement of PFS was shown in the Applicant's registrational trial, and if approved, dacomitinib will be available as another oral based therapy for the treatment of patients with NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutations, as detected by an FDA-approved test.

DRISK and DOP 2 agree that a REMS is not needed to ensure the benefits of dacomitinib outweigh its risks.

9 Conclusion & Recommendations

Based on the available data, a REMS is not necessary for dacomitinib to ensure the benefits outweigh the risks. The safety concerns associated with dacomitinib have been documented with the use of other EGFR TKI therapy, and healthcare providers who treat NSCLC are familiar with the risks of these drugs and the importance of patient monitoring. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile so that this recommendation can be reevaluated if necessary.

10 Appendices

10.1 SAFETY PROFILE OF EGFR TKI THERAPY FOR NSCLC

	Dacomitinib[1]	Gefitinib[6]	Osimertinib[7]	Afatinib[8]	Erlotinib[9]
Approval	Pending 2018	2015	2015	2013	2004
Mutations	EGFR exon 19 deletion or exon 21 L858R substitution	EGFR exon 19 deletion or exon 21 L858R substitution	EGFR T790M	Nonresistant EGFR mutations	EGFR exon 19 deletion or exon 21 L858R substitution
Dose	45 mg orally once daily until disease progression or unacceptable toxicity	250 mg orally once daily until disease progression or unacceptable toxicity	80 mg orally once daily until disease progression or unacceptable toxicity	40mg orally once daily until disease progression or unacceptable toxicity	150mg orally, once daily until disease progression or unacceptable toxicity
REMS?	No	No	No	No	No
Boxed Warning?	No	No	No	No	No
Warnings and Precautions	ILD/pneumonitis (5.1), Diarrhea (5.2), Dermatologic events (5.3), Embryo-fetal toxicity	ILD/pneumonitis (5.1), hepatotoxicity (5.2), Gastrointestinal perforation (5.3), Severe/persistent diarrhea (5.4), Ocular disorders (5.5) Bullous and exfoliative skin disorders (5.6), Embryo-fetal toxicity (5.7)	ILD/pneumonitis (5.1), QTc Interval Prolongation (5.2), Cardiomyopathy (5.3), Embryo-fetal toxicity (5.4)	Diarrhea (5.1), Bullous and exfoliative skin disorders (5.2), ILD/pneumonitis (5.3), Hepatic toxicity (5.4), Keratitis (5.5), Embryo-fetal toxicity (5.6)	ILD (5.1), Renal Failure (5.2), Hepatoxicity (5.3), Gastrointestinal perforation (5.4), Bullous and exfoliative skin disorders (5.5), Cerebrovascular accident (5.6), Microangiopathic hemolytic anemia with thrombocytopenia (5.7), Ocular disorders (5.8), Hemorrhage in patients taking warfarin (5.9), Embryo-fetal toxicity (5.10)

10.2 REFERENCES

[1] Dacomitinib FDA Draft Prescribing Information, June 28, 2018

[2] www.cancer.org/cancer/non-small-cell-lung-cancer/about/key-statistics accessed June 20, 2018

[3] Midha A, Dearden S, McCormack R. EGFR mutation incidence in non-small-cell lung cancer of adenocarcinoma histology: a systematic review and global map by ethnicity. *Am J Cancer Res*. August 15, 2015; 5(9):2892-2911

[4] Hirsch F, Scagliotti G, Mulshine J et al. Lung cancer: current therapies and new targeted treatments. *Lancet* January 2017;389:299-311

[5] Dacomitinib midcycle review clinical slides, slide number 37, April 26, 2018

[6] Iressa (gefitinib) Prescribing Information, July 2015, AstraZeneca Pharmaceuticals

[7] Tagrisso (osimertinib) Prescribing Information, November 2015, AstraZeneca Pharmaceuticals

[8] Gilotrif (afatinib) Prescribing Information, Revised January 2018, approved 2013, Boehringer Ingelheim Pharmaceuticals

[9] Tarceva (erlotinib) Prescribing Information, Revised October 2016, approved 2004, OSI Pharmaceuticals, LLC

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/s/

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