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November 2, 2018 Pfizer Inc. (NYSE:PFE) today announced that the U.S. Food and Drug Administration (FDA) has approved Lorbrena [lor-BREN-ah] (lorlatinib), a third-generation anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI) for patients with ALK-positive metastatic non-small cell lung cancer (NSCLC) whose disease has progressed on crizotinib and at least one other ALK inhibitor for metastatic disease; or whose disease has progressed on alectinib or ceritinib as the first ALK inhibitor therapy for metastatic disease. 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 a confirmatory trial. This represents the third FDA approval Pfizer has received for an

oncology treatment, including two lung cancer medicines, within two months.

“Over the years, Pfizer has transformed research, management and treatment for patients with ALK-positive non-small cell lung cancer.

Building upon our extensive understanding of tumor complexity and

treatment resistance, Lorbrena was discovered by Pfizer scientists and developed specifically to inhibit tumor mutations that may drive

resistance to other ALK tyrosine kinase inhibitors,” said Andy Schmeltz,

Global President, Pfizer Oncology. “We believe that Lorbrena will

benefit patients with ALK-positive metastatic non-small cell lung cancer

that have progressed on prior therapy and continue to deliver on our

commitment to addressing unmet needs of cancer patients.”

Since Pfizer introduced Xalkori (crizotinib) as the first TKI for the treatment of ALK-positive metastatic NSCLC in 2011, the

availability of these medicines has created an opportunity to provide

patients with treatment options other than chemotherapy.

However, lung

cancer remains the leading cause of cancer-related death around the

world.

While many ALK-positive metastatic NSCLC patients respond to initial TKI

therapy, they typically experience tumor progression.^{1,2} Additionally, options for patients who progress after treatment with second-generation ALK TKIs, alectinib, brigatinib and ceritinib, are limited.³ The approval of Lorbrena represents a new option for patients who have progressed on a second-generation ALK TKI, providing an opportunity to remain on oral therapy.

“The last decade has witnessed dramatic improvements in the treatment of metastatic ALK-positive non-small cell lung cancer due to earlier generation ALK biomarker-driven therapies. Yet almost all patients still relapse due to drug resistance, with a large proportion of patients developing new or worsening brain metastases,” said Alice T. Shaw, MD, PhD, Professor of Medicine at Harvard Medical School, and Director of the Center for Thoracic Cancers at Massachusetts General Hospital. “In a clinical study which included patients with or without brain metastases, Lorbrena demonstrated clinical activity in patients with metastatic ALK-positive non-small cell lung cancer who had failed other ALK biomarker-driven therapies.”

The approval was based on a non-randomized, dose-ranging and activity-estimating, multi-cohort, multicenter Phase 1/2 study, B7461001, evaluating Lorbrena for the treatment of patients with

ALK-positive metastatic NSCLC, who were previously treated with one or more ALK TKIs. A total of 215 patients with ALK-positive metastatic NSCLC were enrolled across various subgroups based on prior treatment. Among these patients, overall response rate (ORR) was 48 percent (95% CI: 42%, 55%) and importantly, 57 percent had previous treatment with more than one ALK TKI. In the trial, 69 percent of patients had a history of brain metastases and intracranial response rate was 60 percent (95% CI: 49%, 70%).

“Since leading with the first approval of a biomarker-driven treatment for ALK-positive non-small cell lung cancer in 2011, Pfizer scientists and clinicians have remained committed to researching and developing medicines that can further advance the care of these patients,” said Mace Rothenberg, MD, Chief Development Officer, Oncology, Pfizer Global Product Development. “Lorbrena’s approval is an important milestone for patients, having demonstrated marked activity in a study that included a broad range of individuals with ALK-positive non-small cell lung cancer. This includes patients who were heavily pretreated and facing limited options after receiving first- and second-generation ALK tyrosine kinase inhibitors.”

Among 295 ALK-positive or ROS1-positive metastatic NSCLC patients who received Lorbrena 100 mg once daily in study B7461001, the most common ($\geq 20\%$) adverse reactions were edema, peripheral neuropathy, cognitive effects, dyspnea, fatigue, weight gain, arthralgia, mood effects, and diarrhea. The most common ($\geq 20\%$) laboratory abnormalities were hypercholesterolemia, hypertriglyceridemia, anemia, hyperglycemia, increased AST, hypoalbuminemia, increased ALT, increased lipase, and increased alkaline phosphatase. Serious adverse reactions occurred in 32 percent of the 295 patients. The most frequent serious adverse reactions reported were pneumonia (3.4%), dyspnea (2.7%), pyrexia (2%), mental status changes (1.4%), and respiratory failure (1.4%). Fatal adverse reactions occurred in 2.7 percent of patients and included pneumonia (0.7%), myocardial infarction (0.7%), acute pulmonary edema (0.3%), embolism (0.3%), peripheral artery occlusion (0.3%), and respiratory distress (0.3%). Permanent discontinuation of Lorbrena for adverse reactions occurred in eight percent of patients; approximately 48 percent of patients required dose interruptions and 24 percent required at least one dose reduction.

Pfizer is committed to ensuring that patients living with lung cancer

have access to this innovative therapy. Patients in the U.S. who are prescribed Lorbrena have access to Pfizer Oncology Together™, which offers personalized patient support including financial assistance and additional resources to help them manage day-to-day life with their condition.

About Lorbrena (lorlatinib)

Lorbrena is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) whose disease has progressed on crizotinib and at least one other ALK inhibitor for metastatic disease; or whose disease has progressed on alectinib or ceritinib as the first ALK inhibitor therapy for metastatic disease.

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 a confirmatory trial.

Lorbrena is currently approved in Japan for the treatment of ALK fusion gene-positive unresectable advanced and/or recurrent non-small cell lung cancer with resistance or intolerance to ALK tyrosine kinase inhibitor(s).

IMPORTANT LORBRENA SAFETY INFORMATION

Contraindications: Lorbrena is contraindicated in patients taking strong CYP3A inducers, due to the potential for serious hepatotoxicity.

Risk of Serious Hepatotoxicity with Concomitant Use of Strong CYP3A

Inducers: Severe hepatotoxicity occurred in 10 of 12 healthy subjects receiving a single dose of Lorbrena with multiple daily doses of rifampin, a strong CYP3A inducer. Grade 4 ALT or AST elevations occurred in 50% of subjects, Grade 3 in 33% of subjects, and Grade 2 in 8% of subjects. Discontinue strong CYP3A inducers for 3 plasma half-lives of the strong CYP3A inducer prior to initiating Lorbrena.

Avoid concomitant use of Lorbrena with moderate CYP3A inducers. If concomitant use of moderate CYP3A inducers cannot be avoided, monitor AST, ALT, and bilirubin 48 hours after initiating Lorbrena and at least 3 times during the first week after initiating Lorbrena. Depending upon the relative importance of each drug, discontinue Lorbrena or the CYP3A inducer for persistent Grade 2 or higher hepatotoxicity.

Central Nervous System (CNS) Effects: A broad spectrum of CNS effects can occur. These include seizures, hallucinations, and changes in cognitive function, mood (including suicidal ideation), speech, mental status, and sleep. Withhold and resume at the same or reduced

dose or permanently discontinue based on severity.

Hyperlipidemia: Increases in serum cholesterol and triglycerides can occur. Grade 3 or 4 elevations in total cholesterol occurred in 17% and Grade 3 or 4 elevations in triglycerides occurred in 17% of the 332 patients who received Lorbrena. Eighty percent of patients required initiation of lipid-lowering medications, with a median time to onset of start of such medications of 21 days. Initiate or increase the dose of lipid-lowering agents in patients with hyperlipidemia. Monitor serum cholesterol and triglycerides before initiating Lorbrena, 1 and 2 months after initiating Lorbrena, and periodically thereafter. Withhold and resume at same dose for the first occurrence; resume at same or reduced dose of Lorbrena for recurrence based on severity.

Atrioventricular (AV) Block: PR interval prolongation and AV block can occur. In 295 patients who received Lorbrena at a dose of 100 mg orally once daily and who had a baseline electrocardiography (ECG), 1% experienced AV block and 0.3% experienced Grade 3 AV block and underwent pacemaker placement. Monitor ECG prior to initiating Lorbrena and periodically thereafter. Withhold and resume at reduced or same dose in patients who undergo pacemaker placement. Permanently discontinue for

recurrence in patients without a pacemaker.

Interstitial Lung Disease (ILD)/Pneumonitis: Severe or life-threatening pulmonary adverse reactions consistent with ILD/pneumonitis can occur. ILD/pneumonitis occurred in 1.5% of patients, including Grade 3 or 4 ILD/pneumonitis in 1.2% of patients. Promptly investigate for ILD/pneumonitis in any patient who presents with worsening of respiratory symptoms indicative of ILD/pneumonitis. Immediately withhold Lorbrena in patients with suspected ILD/pneumonitis. Permanently discontinue Lorbrena for treatment-related ILD/pneumonitis of any severity.

Embryo-fetal Toxicity: Lorbrena can cause fetal harm. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use an effective non-hormonal method of contraception, since Lorbrena can render hormonal contraceptives ineffective, during treatment with Lorbrena and for at least 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with Lorbrena and for 3 months after the final dose.

Adverse Reactions: Serious adverse reactions occurred in 32% of the 295 patients; the most frequently reported serious adverse reactions were pneumonia (3.4%), dyspnea (2.7%), pyrexia (2%), mental status

changes (1.4%), and respiratory failure (1.4%). Fatal adverse reactions occurred in 2.7% of patients and included pneumonia (0.7%), myocardial infarction (0.7%), acute pulmonary edema (0.3%), embolism (0.3%), peripheral artery occlusion (0.3%), and respiratory distress (0.3%). The most common ($\geq 20\%$) adverse reactions were edema, peripheral neuropathy, cognitive effects, dyspnea, fatigue, weight gain, arthralgia, mood effects, and diarrhea; the most common ($\geq 20\%$) laboratory abnormalities were hypercholesterolemia, hypertriglyceridemia, anemia, hyperglycemia, increased AST, hypoalbuminemia, increased ALT, increased lipase, and increased alkaline phosphatase.

Drug Interactions: Lorbrena is contraindicated in patients taking strong CYP3A inducers. Avoid concomitant use with moderate CYP3A inducers and strong CYP3A inhibitors. If concomitant use of moderate CYP3A inducers cannot be avoided, monitor ALT, AST, and bilirubin as recommended. If concomitant use with a strong CYP3A inhibitor cannot be avoided, reduce the Lorbrena dose as recommended. Concomitant use of Lorbrena decreases the concentration of CYP3A substrates.

Lactation: Because of the potential for serious adverse reactions in breastfed infants, instruct women not to breastfeed during

treatment

with Lorbreina and for 7 days after the final dose.

Hepatic Impairment: No dose adjustment is recommended for patients with mild hepatic impairment. The recommended dose of Lorbreina has not been established for patients with moderate or severe hepatic impairment.

Renal Impairment: No dose adjustment is recommended for patients with mild or moderate renal impairment. The recommended dose of Lorbreina has not been established for patients with severe renal impairment.

About Non-Small Cell Lung Cancer

Lung cancer is the leading cause of cancer death worldwide.⁴ NSCLC accounts for about 85 percent of lung cancer cases and remains difficult to treat, particularly in the metastatic setting.⁵ Approximately 75 percent of NSCLC patients are diagnosed late with metastatic or advanced disease where the five-year survival rate is only five percent.^{2,6,7}

ALK gene rearrangement is a genetic alteration that drives the development of lung cancer in some patients.^{8,9} Epidemiology studies suggest that approximately three to five percent of NSCLC tumors are ALK-positive.^{10,11}

About Pfizer in Lung Cancer

Pfizer Oncology is committed to addressing the unmet needs of patients with lung cancer, the leading cause of cancer-related deaths worldwide and a particularly difficult-to-treat disease. Pfizer strives to address the diverse and evolving needs of patients with non-small cell lung cancer (NSCLC) by developing efficacious and tolerable therapies, including biomarker-driven therapies and immuno-oncology (IO) agents and combinations. By combining leading scientific insights with a patient-centric approach, Pfizer is continually advancing its work to match the right patient with the right medicine at the right time. Through our growing research pipeline and collaboration efforts, we are committed to delivering renewed hope to patients living with NSCLC.

About Pfizer Oncology

At Pfizer Oncology, we are committed to advancing medicines wherever we believe we can make a meaningful difference on the lives of patients. Today, Pfizer Oncology has an industry-leading portfolio of 13 approved cancer medicines across 21 indications, including breast, prostate, kidney, lung and hematology. We also have one of the deepest oncology

biosimilars pipelines, with two medicines approved globally and several assets in mid to late-stage development for the treatment of cancer or as supportive care. Pfizer Oncology is striving to change the trajectory of cancer.

Pfizer Inc: Working together for a healthier world®

At Pfizer, we apply science and our global resources to bring therapies to people that extend and significantly improve their lives. We strive to set the standard for quality, safety and value in the discovery, development and manufacture of health care products. Our global portfolio includes medicines and vaccines as well as many of the world's best-known consumer health care products. Every day, Pfizer colleagues work across developed and emerging markets to advance wellness, prevention, treatments and cures that challenge the most feared diseases of our time. Consistent with our responsibility as one of the world's premier innovative biopharmaceutical companies, we collaborate with health care providers, governments and local communities to support and expand access to reliable, affordable health care around the world. For more than 150 years, we have worked to make a difference for

all who
rely on us. We routinely post information that may be
important to
investors on our website at www.pfizer.com. In
addition, to learn more, please visit us on www.pfizer.com
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is as of
November 2, 2018. Pfizer assumes no obligation to update
forward-looking
statements contained in this release as the result of new
information or
future events or developments.*

*This release contains forward-looking information about
Lorbrena
(lorlatinib), including its potential benefits, that involves
substantial risks and uncertainties that could cause actual
results to
differ materially from those expressed or implied by such
statements.*

*Risks and uncertainties include, among other things,
uncertainties
regarding the commercial success of Lorbrena; the
uncertainties inherent
in research and development, including the ability to meet
anticipated
clinical trial commencement and completion dates and
regulatory
submission dates, as well as the possibility of unfavorable
clinical
trial results, including unfavorable new clinical data and
additional*

analyses of existing clinical data; whether and when applications for Lorbrena may be filed in any other jurisdictions; whether and when any such applications for Lorbrena that maybe be pending or filed may be approved by regulatory authorities, which will depend on the assessment by such regulatory authorities of the benefit-risk profile suggested by the totality of the efficacy and safety information submitted and, if approved, whether Lorbrena will be commercially successful; decisions by regulatory authorities regarding labeling and other matters that could affect the availability or commercial potential of Lorbrena; and competitive developments.

A further description of risks and uncertainties can be found in Pfizer's Annual Report on Form 10-K for the fiscal year ended December 31, 2017 and in its subsequent reports on Form 10-Q, including in the sections thereof captioned "Risk Factors" and "Forward-Looking Information and Factors That May Affect Future Results", as well as in its subsequent reports on Form 8-K, all of which are filed with the U.S. Securities and Exchange Commission and available at www.sec.gov and www.pfizer.com.

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Lorbrena (lorlatinib) FDA Approval History