U.S. FDA Approves LORBRENA® (lorlatinib) for Previously-Treated ALK-Positive Metastatic NSCLC

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LORBRENA Addresses Unmet Needs for Certain Patients Treated With Prior ALK Therapy

NEW YORK--(BUSINESS WIRE)--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 (≥ 20%) adverse reactions were edema, peripheral neuropathy, cognitive effects, dyspnea, fatigue, weight gain, arthralgia, mood effects, and diarrhea. The most common (≥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. The full prescribing information for LORBRENA can be found here.

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 TogetherTM, 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 FROM THE U.S. PRESCRIBING 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 (≥20%) adverse reactions were edema, peripheral neuropathy, cognitive effects, dyspnea, fatigue, weight gain, arthralgia, mood effects, and diarrhea; the most common (≥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 LORBRENA 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 LORBRENA 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 LORBRENA 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 XALKORI® (crizotinib)

XALKORI is a tyrosine kinase inhibitor (TKI) indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK) or ROS1-positive as detected by an FDA-approved test. XALKORI has

received approval for patients with ALK-positive NSCLC in more than 90 countries including Australia, Canada, China, Japan, South Korea and the European Union. XALKORI is also approved for ROS1-positive NSCLC in more than 60 countries.

XALKORI® Important Safety Information

Hepatotoxicity: Drug-induced hepatotoxicity with fatal outcome occurred in 0.1% of patients treated with XALKORI across clinical trials (n=1719). Transaminase elevations generally occurred within the first 2 months. Monitor liver function tests, including ALT, AST, and total bilirubin, every 2 weeks during the first 2 months of treatment, then once a month, and as clinically indicated, with more frequent repeat testing for increased liver transaminases, alkaline phosphatase, or total bilirubin in patients who develop transaminase elevations. Permanently discontinue for ALT/AST elevation >3 times ULN with concurrent total bilirubin elevation >1.5 times ULN (in the absence of cholestasis or hemolysis); otherwise, temporarily suspend and dose-reduce XALKORI as indicated.

Interstitial Lung Disease (Pneumonitis): Severe, life-threatening, or fatal interstitial lung disease (ILD)/pneumonitis can occur. Across clinical trials (n=1719), 2.9% of XALKORI-treated patients had any grade ILD, 1.0% had Grade 3/4, and 0.5% had fatal ILD. ILD generally occurred within 3 months after initiation of treatment. Monitor for pulmonary symptoms indicative of ILD/pneumonitis. Exclude other potential causes and permanently discontinue XALKORI in patients with drug-related ILD/pneumonitis.

QT Interval Prolongation: QTc prolongation can occur. Across clinical trials (n=1616), 2.1% of patients had QTcF (corrected QT by the Fridericia method) ≥500 ms and 5.0% had an increase from baseline QTcF ≥60 ms by automated machine-read evaluation of ECGs. Avoid use in patients with congenital long QT syndrome. Monitor ECGs and electrolytes in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or who are taking medications that prolong the QT interval. Permanently discontinue XALKORI in patients who develop QTc >500 ms or ≥60 ms change from baseline with Torsade de pointes, polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia. Withhold XALKORI in patients who develop QTc >500 ms on at least 2 separate ECGs until recovery to a QTc ≤480 ms, then resume at a reduced dose.

Bradycardia: Symptomatic bradycardia can occur. Across clinical trials, bradycardia occurred in 12.7% of patients treated with XALKORI (n=1719). Avoid use in combination with other agents known to cause bradycardia. Monitor heart rate and blood pressure regularly. In cases of symptomatic bradycardia that is not life-threatening, hold XALKORI

until recovery to asymptomatic bradycardia or to a heart rate of ≥60 bpm, re-evaluate the use of concomitant medications, and adjust the dose of XALKORI. Permanently discontinue for life-threatening bradycardia due to XALKORI; however, if associated with concomitant medications known to cause bradycardia or hypotension, hold XALKORI until recovery to asymptomatic bradycardia or to a heart rate of ≥60 bpm. If concomitant medications can be adjusted or discontinued, restart XALKORI at 250 mg once daily with frequent monitoring.

Severe Visual Loss: Across clinical trials, the incidence of Grade 4 visual field defect with vision loss was 0.2% (n=1719). Discontinue XALKORI in patients with new onset of severe visual loss (best corrected vision less than 20/200 in one or both eyes). Perform an ophthalmological evaluation. There is insufficient information to characterize the risks of resumption of XALKORI in patients with a severe visual loss; a decision to resume should consider the potential benefits to the patient.

Vision Disorders: Most commonly visual impairment, photopsia, blurred vision or vitreous floaters, occurred in 63.1% of 1719 patients. The majority (95%) of these patients had Grade 1 visual adverse reactions. 0.8% of patients had Grade 3 and 0.2% had Grade 4 visual impairment. The majority of patients on the XALKORI arms in Studies 1 and 2 (>50%) reported visual disturbances which occurred at a frequency of 4-7 days each week, lasted up to 1 minute, and had mild or no impact on daily activities.

Embryo-Fetal Toxicity: XALKORI can cause fetal harm when administered to a pregnant woman. Advise of the potential risk to the fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment and for at least 45 days (females) or 90 days (males) respectively, following the final dose of XALKORI.

ROS1-positive Metastatic NSCLC: Safety was evaluated in 50 patients with ROS1-positive metastatic NSCLC from a single-arm study, and was generally consistent with the safety profile of XALKORI evaluated in patients with ALK-positive metastatic NSCLC. Vision disorders occurred in 92% of patients in the ROS1 study; 90% of patients had Grade 1 vision disorders and 2% had Grade 2.

Adverse Reactions: Safety was evaluated in a phase 3 study in previously untreated patients with ALK-positive metastatic NSCLC randomized to XALKORI (n=171) or chemotherapy (n=169). Serious adverse events were reported in 34% of patients treated with XALKORI, the most frequent were dyspnea (4.1%) and pulmonary embolism (2.9%). Fatal adverse events in XALKORI-treated patients occurred in 2.3% of patients, consisting

of septic shock, acute respiratory failure, and diabetic ketoacidosis. Common adverse reactions (all grades) occurring in ≥25% and more commonly (≥5%) in patients treated with XALKORI vs chemotherapy were vision disorder (71% vs 10%), diarrhea (61% vs 13%), edema (49% vs 12%), vomiting (46% vs 36%), constipation (43% vs 30%), upper respiratory infection (32% vs 12%), dysgeusia (26% vs 5%), and abdominal pain (26% vs 12%). Grade 3/4 reactions occurring at a ≥2% higher incidence with XALKORI vs chemotherapy were QT prolongation (2% vs 0%), esophagitis (2% vs 0%), and constipation (2% vs 0%). In patients treated with XALKORI vs chemotherapy, the following occurred: elevation of ALT (any grade [79% vs 33%] or Grade 3/4 [15% vs 2%]); elevation of AST (any grade [66% vs 28%] or Grade 3/4 [8% vs 1%]); neutropenia (any grade [52% vs 59%] or Grade 3/4 [11% vs 16%]); lymphopenia (any grade [48% vs 53%] or Grade 3/4 [7% vs 13%]); hypophosphatemia (any grade [32% vs 21%] or Grade 3/4 [10% vs 6%]). In patients treated with XALKORI vs chemotherapy, renal cysts occurred (5% vs 1%). Nausea (56%), decreased appetite (30%), fatigue (29%), and neuropathy (21%) also occurred in patients taking XALKORI.

Drug Interactions: Exercise caution with concomitant use of moderate CYP3A inhibitors. Avoid grapefruit or grapefruit juice which may increase plasma concentrations of crizotinib. Avoid concomitant use of strong CYP3A inducers and inhibitors. Avoid concomitant use of CYP3A substrates with narrow therapeutic range in patients taking XALKORI. If concomitant use of CYP3A substrates with narrow therapeutic range is required in patients taking XALKORI, dose reductions of the CYP3A substrates may be required due to adverse reactions.

Lactation: Because of the potential for adverse reactions in breastfed infants, advise females not to breastfeed during treatment with XALKORI and for 45 days after the final dose.

Hepatic Impairment: Crizotinib concentrations increased in patients with pre-existing moderate (any AST and total bilirubin >1.5x ULN and ≤3x ULN) or severe (any AST and total bilirubin >3x ULN) hepatic impairment. Reduce XALKORI dose in patients with moderate or severe hepatic impairment. The recommended dose of XALKORI in patients with pre-existing moderate hepatic impairment is 200 mg orally twice daily or with pre-existing severe hepatic impairment is 250 mg orally once daily.

Renal Impairment: Decreases in estimated glomerular filtration rate occurred in patients treated with XALKORI. Administer XALKORI at a starting dose of 250 mg taken orally once daily in patients with severe renal impairment (CLcr <30 mL/min) not requiring dialysis.

For more information and full prescribing information, please visit www.XALKORI.com.

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 and follow us on Twitter at @Pfizer and @Pfizer_News, LinkedIn, YouTube, and like us on Facebook at Facebook.com/Pfizer.

DISCLOSURE NOTICE: The information contained in this release 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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