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U.S. FDA Expands Approval of Pfizer's LORBRENA® as First-Line Treatment for ALK-Positive Metastatic Lung Cancer

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Approval is based on CROWN trial, which showed a 72% reduction in risk of progression or death for treatment with LORBRENA vs. XALKORI®

NEW YORK--(BUSINESS WIRE)-- The U.S. Food and Drug Administration (FDA) approved Pfizer Inc.'s (NYSE: PFE) supplemental New Drug Application (sNDA) for LORBRENA® (lorlatinib), expanding the indication to include first-line treatment of people with anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC). LORBRENA is now indicated for adults with metastatic NSCLC whose tumors are ALK-positive as detected by an FDA-approved test. The FDA action also converts the 2018 accelerated approval to full approval. The application was approved under the FDA's Real-Time Oncology Review (RTOR) pilot program.

"For more than a decade, Pfizer has been a pioneer in delivering biomarker-driven therapies and addressing the diverse and evolving needs of people with non-small cell lung cancer," said Andy Schmeltz, Global President, Pfizer Oncology. "LORBRENA has been a transformative medicine for people with ALK-positive advanced NSCLC, and this FDA approval in the first-line setting means that we can now extend hope to even more people."

LORBRENA is a third-generation ALK inhibitor specifically designed to inhibit the most common tumor mutations that drive resistance to current medications and to address metastases in the brain, a frequent site for disease progression in ALK-positive NSCLC. Up to 40% of people with ALK-positive metastatic NSCLC present with brain metastases at initial diagnosis.[1,2,3]

The expanded approval of LORBRENA is based on the results from the pivotal Phase 3 CROWN trial, which showed a 72% reduction in risk of progression or death vs. XALKORI® (crizotinib) in a previously untreated patient population (HR 0.28: 95% CI, 0.19 to 0.41; $p<0.0001$) as assessed by blinded independent central review (BICR). Central nervous system (CNS) involvement was assessed in all patients. There were 17 patients in the LORBRENA arm and 13 in the XALKORI arm with measurable brain metastases based on baseline brain imaging. A prespecified exploratory analysis showed that among these patients, the intracranial objective response rate (IC-ORR), as assessed by BICR, was 82% (95% CI, 57 to 96) in the LORBRENA arm and 23% (95% CI, 5 to 54) in the XALKORI arm. The intracranial duration of response (IC-DOR) was 12 months or longer in 79% (n=11) and 0% of patients in the LORBRENA and XALKORI arms, respectively.

The most common adverse events (AEs) of any Grade and Grade 3-4 worsening laboratory abnormalities occurring in ?20% of people treated with LORBRENA were edema (56%), weight gain (38%), peripheral

neuropathy (35%), cognitive effects (21%), diarrhea (21%), dyspnea (20%), and hypertriglyceridemia (22%). Serious AEs occurred in 34% of people treated with LORBRENA; the most frequently reported serious AEs were pneumonia (4.7%), dyspnea (2.7%), respiratory failure (2.7%), cognitive effects (2.0%), and pyrexia (2.0%). Fatal AEs occurred in 3.4% of people treated with LORBRENA and included pneumonia (0.7%), respiratory failure (0.7%), cardiac failure acute (0.7%), pulmonary embolism (0.7%), and sudden death (0.7%). Permanent discontinuation of LORBRENA due to AEs occurred in 6.7% of people. AEs leading to dose interruptions and dose reductions occurred in 49% and 21% of people treated with LORBRENA, respectively. Detailed results from the CROWN study were published in the November 2020 issue of the *New England Journal of Medicine*.

“The CROWN data have shown LORBRENA can significantly improve outcomes in the first-line treatment of ALK-positive non-small cell lung cancer, including those that present with brain metastases,” said Benjamin Solomon, M.D., Department of Medical Oncology, Peter MacCallum Cancer Centre. “This approval is meaningful for my patients because we now have a highly effective treatment option that can delay the progression of a typically aggressive disease.”

In 2018, the FDA approved LORBRENA for the treatment of patients with ALK-positive metastatic 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 was approved under accelerated approval based on tumor response rate and duration of response. Based on the CROWN data, the FDA has also converted the accelerated approval to full approval.

This sNDA was also reviewed by the FDA under Project ORBIS, an initiative introduced in 2019, which provides a framework for potential concurrent submissions and collaborative review with health authorities in Canada, Singapore, Switzerland, Australia, Brazil and the United Kingdom. Under Project ORBIS, collaboration among international regulators may allow people with cancer to receive earlier access to products in other countries. The European Medicines Agency is also reviewing a Type II variation application for LORBRENA in the first line indication.

About the CROWN Trial

CROWN is a Phase 3, randomized, open-label, parallel 2-arm trial in which 296 people with previously untreated advanced ALK-positive NSCLC were randomized 1:1 to receive LORBRENA monotherapy (n=149) or XALKORI monotherapy (n=147). Patients were required to have an ECOG performance status of 0-2 and ALK-positive NSCLC as identified by the VENTANA ALK (D5F3) CDx assay. The primary endpoint of the CROWN trial is PFS based on BICR. Secondary endpoints include overall survival (OS) and tumor assessment related data by BICR, including ORR, and DOR. In patients with measurable CNS metastases at baseline, additional outcome measures were IC-ORR and IC-DOR by BICR.

About Non-Small Cell Lung Cancer (NSCLC)

Lung cancer is the number one cause of cancer-related death around the world.[4] NSCLC accounts for approximately 80-85% of lung cancers,[5] with ALK-positive tumors occurring in about 3-5% of NSCLC cases.[6] In 2020, an estimated 228,820 new cases of lung cancer were diagnosed in the U.S.[7]

About LORBRENA® (lorlatinib)

LORBRENA is a tyrosine kinase inhibitor (TKI) that has been shown to be highly active in preclinical lung cancer models harboring chromosomal rearrangements of ALK. LORBRENA was specifically developed to inhibit tumor mutations that drive resistance to other ALK inhibitors and to penetrate the blood brain barrier.

LORBRENA is approved in the U.S. for the treatment of adults with metastatic NSCLC whose tumors are ALK-positive as detected by an FDA-approved test.

IMPORTANT LORBRENA® (lorlatinib) 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. ALT or AST elevations occurred within 3 days and returned to within normal limits after a median of 15 days (7 to 34 days); median time to recovery in subjects with Grade 3 or 4 or Grade 2 ALT or AST elevations was 18 days and 7 days, respectively. LORBRENA is contraindicated in patients taking strong CYP3A inducers. Discontinue strong CYP3A inducers for 3 plasma half-lives of the strong CYP3A inducer prior to initiating LORBRENA.

Central Nervous System (CNS) Effects: A broad spectrum of CNS effects can occur; overall, CNS effects occurred in 52% of the 476 patients receiving LORBRENA. These included seizures (1.9%, sometimes in conjunction with other neurologic findings), psychotic effects (7%; 0.6% severe [Grade 3 or 4]), and changes in cognitive function (28%; 2.9% severe), mood (including suicidal ideation) (21%; 1.7% severe), speech (11%; 0.6% severe), mental status (1.3%; 1.1% severe), and sleep (12%). Median time to first onset of any CNS effect was 1.4 months (1 day to 3.4 years). Overall, 2.1% and 10% of patients required permanent or temporary discontinuation of LORBRENA, respectively, for a CNS effect; 8% required dose reduction. Withhold and resume at 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 18% and Grade 3 or 4 elevations in triglycerides occurred in 19% of the 476 patients who received LORBRENA. Median time to onset was 15 days for both hypercholesterolemia and hypertriglyceridemia. Approximately 4% and 7% of patients required temporary discontinuation and 1% and 3% of patients required dose reduction of LORBRENA for elevations in cholesterol and in triglycerides in Study B7461001 and Study B7461006, respectively. Eighty-three percent of patients required initiation of lipid-lowering medications, with a median time to onset of start of such medications of 17 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 476 patients who received LORBRENA at a dose of 100 mg orally once daily and who had a baseline electrocardiography (ECG), 1.9% experienced AV block and 0.2% 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 1.9% of patients, including Grade 3 or 4 ILD/pneumonitis in 0.6% of patients. Four patients (0.8%) discontinued LORBRENA for ILD/pneumonitis. Promptly investigate for ILD/pneumonitis in any patient who presents with worsening of respiratory symptoms

indicative of ILD/pneumonitis (e.g., dyspnea, cough, and fever). Immediately withhold LORBRENA in patients with suspected ILD/pneumonitis. Permanently discontinue LORBRENA for treatment-related ILD/pneumonitis of any severity.

Hypertension: Hypertension can occur in patients receiving LORBRENA. Hypertension occurred in 13% of patients, including Grade 3 or 4 in 6% of patients. Median time to onset of hypertension was 6.4 months (1 day to 2.8 years). 2.3% of patients temporarily discontinued LORBRENA for hypertension. Control blood pressure prior to initiating LORBRENA. Monitor blood pressure after 2 weeks and at least monthly thereafter. Withhold and resume at reduced dose or permanently discontinue based on severity.

Hyperglycemia: Hyperglycemia can occur in patients receiving LORBRENA. Hyperglycemia occurred in 9% of patients, including Grade 3 or 4 in 3.2% of patients. Median time to onset of hyperglycemia was 4.8 months (1 day to 2.9 years). 0.8% of patients temporarily discontinued LORBRENA for hyperglycemia. Assess fasting serum glucose prior to initiating LORBRENA and monitor periodically thereafter. Withhold and resume at reduced dose or permanently discontinue based on 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: In the pooled safety population of 476 patients who received 100 mg LORBRENA once daily, the most frequent (? 20%) adverse reactions were edema (56%), peripheral neuropathy (44%), weight gain (31%), cognitive effects (28%), fatigue (27%), dyspnea (27%), arthralgia (24%), diarrhea (23%), mood effects (21%), and cough (21%). The most frequent (? 20%) laboratory abnormalities in patients receiving LORBRENA were hypercholesterolemia (21%) and hypertriglyceridemia (21%).

In previously untreated patients, serious adverse reactions occurred in 34% of the 149 patients treated with LORBRENA; the most frequently reported serious adverse reactions were pneumonia (4.7%), dyspnea (2.7%), respiratory failure (2.7%), cognitive effects (2.0%), and pyrexia (2.0%). Fatal adverse reactions occurred in 3.4% of patients and included pneumonia (0.7%), respiratory failure (0.7%), cardiac failure acute (0.7%), pulmonary embolism (0.7%), and sudden death (0.7%). In previously treated patients, 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%).

Drug Interactions: LORBRENA is contraindicated in patients taking strong CYP3A inducers. Avoid concomitant use with moderate CYP3A inducers, strong CYP3A inhibitors, and fluconazole. If concomitant use of moderate CYP3A inducers cannot be avoided, increase the LORBRENA dose as recommended. If concomitant use with a strong CYP3A inhibitor or fluconazole cannot be avoided, reduce the LORBRENA dose as recommended. Avoid concomitant use of LORBRENA with CYP3A substrates and P-gp substrates, which may reduce the efficacy of these 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: Reduce the dose of LORBRENA for patients with severe renal impairment. No dose adjustment is recommended for patients with mild or moderate renal impairment.

The full prescribing information for LORBRENA can be found here.

About Pfizer Oncology

At Pfizer Oncology, we are committed to advancing medicines wherever we believe we can make a meaningful difference in the lives of people living with cancer. Today, we have an industry-leading portfolio of 24 approved innovative cancer medicines and biosimilars across more than 30 indications, including breast, genitourinary, colorectal, blood and lung cancers, as well as melanoma.

About Pfizer: Breakthroughs That Change Patients' Lives

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, including innovative medicines and vaccines. 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 170 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 March 3, 2021. 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) and an expanded indication in the U.S. to include first-line treatment of people with anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer, including their 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 endpoints, commencement and/or completion dates for our clinical trials, regulatory submission dates, regulatory approval dates and/or launch dates, as well as the possibility of unfavorable new clinical data and further analyses of existing clinical data; the risk that clinical trial data are subject to differing interpretations and assessments by regulatory authorities; whether regulatory authorities will be satisfied with the design of and results from our clinical studies; whether and when any drug applications may be filed in any additional jurisdictions for LORBRENA for the expanded indication or in any jurisdictions for any other potential indications for LORBRENA; whether and when any such other applications may be approved by regulatory authorities (including the Type II variation application pending in the European Union), which will depend on a myriad factors, including making a determination as to whether the product's benefits outweigh its known risks and determination of the product's efficacy and, if approved, whether such product candidate will be commercially successful; decisions by regulatory authorities impacting labeling, manufacturing processes, safety and/or other matters that could affect the availability or commercial potential of LORBRENA; uncertainties regarding the

impact of COVID-19 on Pfizer's business, operations and financial results; 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, 2020 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.

[1] Peters S. Alectinib versus crizotinib in untreated ALK-positive non–small-cell lung cancer. *N Engl J Med*. 2017;377:829-38?.

[2] Soria JC, Tan DSW, Chiari R, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALKrearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. *Lancet*. 2017;389:917–929.

[3] Gainor JF, Tseng D, Yoda S, et al. Patterns of metastatic spread and mechanisms of resistance to crizotinib in ROS1-positive non-small-cell lung cancer. *JCO Precis Oncol*. 2017;2017.

[4] World Health Organization. International Agency for Research on Cancer. GLOBOCAN 2018: Lung fact sheet. http://gco.iarc.fr/today/data/factsheets/cancers/15-Lung-fact-sheet.pdf. Accessed January 2021.

[5] American Cancer Society. What is lung cancer? https://www.cancer.org/cancer/lung-cancer/about/what-is.html . Accessed February 2021.

[6] Garber K. ALK, lung cancer, and personalized therapy: portent of the future? J Natl Cancer Inst. 2010;102:672-675.

[7] National Cancer Institute. Cancer Stat Facts: Lung and bronchus cancer. https://seer.cancer.gov/statfacts/html/lungb.html. Accessed February 2021.

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