European Commission Approves LORVIQUA® (lorlatinib) for Certain Adult Patients with Previously-Treated ALK-Positive Advanced Non-Small Cell Lung Cancer

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Pfizer Inc. (NYSE: PFE) today announced that the European Commission (EC) granted conditional marketing authorization for LORVIQUA® (lorlatinib, available in the U.S., Canada and Japan under the brand name LORBRENA®), as a monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) whose disease has progressed after alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy, or crizotinib and at least one other ALK TKI. LORVIQUA is a third-generation ALK TKI that was specifically developed to penetrate the blood brain barrier, in the presence or absence of resistance mutations.

“Pfizer has worked to pioneer biomarker-driven medicine for patients with ALK-positive non-small cell lung cancer and we continue to advance patient care with the approval of LORVIQUA,” said Andreas Penk, M.D., regional president, Oncology International Developed Markets at Pfizer. “We are proud that LORVIQUA is our second lung cancer medication approved in Europe within two months and our third biomarker-driven medicine for lung cancer. We look forward to making LORVIQUA available for European patients with ALK-positive non-small cell lung cancer who have progressed on prior therapy with a second generation ALK medicine.”

The conditional marketing authorization was based on results from a non-randomized, dose-ranging and activity-estimating, multi-cohort, multi-center Phase 1/2 study, B7461001, evaluating LORVIQUA for the treatment of patients with ALK-positive advanced NSCLC, who were previously treated with one or more ALK TKIs. A total of 139 patients with ALK-positive metastatic NSCLC after treatment with at least one second-generation ALK TKI, such as alectinib, brigatinib or ceritinib, were enrolled in the Phase 2 portion of the study. Among these patients, the overall response rate (ORR) for those who have been treated with one prior ALK TKI (N=28) was 42.9% (95% CI: 24.5, 62.8) and 39.6% (95% CI: 30.5, 49.4) for those with two or more prior ALK TKI treatments (N=111). In the trial, 67% of patients had a history of brain metastases.

“Over the last decade, our understanding of ALK-positive non-small cell lung cancer has advanced dramatically, leading to multiple medications for patients. However, the common challenges associated with treating the disease, including resistance and brain metastases have created an urgent need for additional treatment options,” said Enriqueta Felip, M.D., Ph.D., Vall d’Hebron University Hospital, Vall d’Hebron Institute of Oncology in Spain. “The LORVIQUA approval marks an exciting time in lung cancer innovation and I look forward to using this next-generation ALK inhibitor to treat my patients.”

Among 295 ALK-positive or ROS1-positive metastatic NSCLC patients who received LORVIQUA 100 mg once daily in study B7461001, the most common (≥ 20%) adverse reactions were hypercholesterolemia (84.4%), hypertriglyceridemia (67.1%), edema (54.6%), peripheral neuropathy (47.8%), cognitive effects (28.8%), fatigue (28.1%), weight increased (26.4%), arthralgia (24.7%), mood effects (22.7%) and diarrhea (22.7%).

Conditional approval is granted to a medicinal product that fulfils an unmet medical need, where the benefit-risk balance is positive and the benefit of the product’s immediate availability outweighs the risk of less comprehensive data than normally required.1 Under the provisions of the conditional approval, Pfizer will provide additional data from the post-marketing studies, including the Phase 3 CROWN study of LORVIQUA versus crizotinib in the first-line treatment of patients with ALK-positive NSCLC, which is currently ongoing.

About LORVIQUA® (lorlatinib)

LORVIQUA is a TKI that has been shown to be highly active in preclinical lung cancer models harboring chromosomal rearrangements of ALK. LORVIQUA was specifically

developed to inhibit tumor mutations that drive resistance to other ALK inhibitors and to penetrate the blood brain barrier. LORVIQUA is approved in the EU as monotherapy for the treatment of adult patients with ALK-positive advanced NSCLC whose disease has progressed after:

alectinib or ceritinib as the first ALK TKI therapy; or crizotinib and at least one other ALK TKI.
LORVIQUA is also approved:

Under the brand name LORBRENA® in Japan for the treatment of ALK fusion gene-positive unresectable advanced and/or recurrent NSCLC with resistance or intolerance to ALK tyrosine kinase inhibitor(s). Under the brand name LORBRENA® in Canada, where it is conditionally approved as monotherapy for the treatment of adult patients with ALK-positive metastatic NSCLC who have progressed on: crizotinib and at least one other ALK inhibitor, or patients who have progressed on ceritinib or alectinib. Under the brand name LORBRENA® in the U.S. 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 alectinib as the first ALK inhibitor therapy for metastatic disease; or ceritinib as the first ALK inhibitor therapy for metastatic disease.
The U.S. 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® (lorlatinib) IMPORTANT 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.

Please see full prescribing information for LORBRENA in the U.S. here.

About Non-Small Cell Lung Cancer

Lung cancer is the most common cancer worldwide, with more than two million new cases diagnosed globally in 2018.2 About 85 percent of all lung cancers are identified as non-small cell, and approximately 75 percent of these are metastatic, or advanced, at diagnosis.3

ALK gene rearrangement is a genetic alteration that drives the development of lung cancer in some patients.4,5 Epidemiology studies suggest that approximately three to five percent of NSCLC tumors are ALK-positive.6

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 18 approved innovative cancer medicines and biosimilars across more than 20 indications, including breast, prostate, kidney, lung and hematology. 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 May 7, 2019. 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 LORVIQUA (lorlatinib), a kinase inhibitor, and an approval by the European Commission, including the potential benefits, that involve 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, 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 applications for LORVIQUA may be filed in other jurisdictions; whether and when any such other applications for LORVIQUA that may be pending or filed may be approved by regulatory authorities, which will depend on 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 LORVIQUA 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 LORVIQUA; 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, 2018 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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1 European Medicines Agency. Conditional Marketing Authorisation. https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation. Accessed March 2019.

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