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Pfizer’s XALKORI® Receives Conditional Marketing Authorization from the European Commission for the Treatment of Adults with Previously Treated ALK-Positive Advanced Non-Small Cell Lung Cancer in the EU

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"Today’s approval is a significant milestone for adults with ALK-positive advanced NSCLC in Europe,"

(BUSINESS WIRE)--Pfizer Inc. announced today that the European Commission has given conditional marketing authorization for XALKORI® (crizotinib) in the European Union (EU) for the treatment of adults with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).

“In the field of metastatic non-small cell lung cancer, XALKORI represents a major advancement. It brings to the patients with ALK-translocated tumors an oral compound that can achieve tumor shrinkage and delay disease progression,” said Dr. Jean-Charles Soria, professor of Medicine and Medical Oncology at South-Paris University and cancer specialist at Institut Gustave Roussy, France.

Similar to accelerated approvals in the United States, conditional marketing authorizations in the EU are granted to medicinal products with a positive benefit/risk assessment that address unmet medical needs and whose availability would result in a significant public health benefit. A conditional marketing authorization is renewable annually. Now that XALKORI has been granted a conditional marketing authorization, Pfizer will be required to submit data to the European Medicines Agency (EMA) from the recently completed PROFILE 1007 study, which was presented in September at the ESMO 2012 Congress in Vienna, Austria. The study met its primary endpoint in previously treated ALK-positive advanced NSCLC patients. Following review of the 1007 results by the EMA’s Committee for Medicinal Products for Human Use (CHMP), the European Commission will consider converting the conditional marketing authorization to a normal marketing authorization.

“Today’s approval is a significant milestone for adults with ALK-positive advanced NSCLC in Europe,” said Dr. Andreas Penk, president of Pfizer Oncology Europe. “XALKORI is a first-in-class medicine and demonstrates Pfizer’s commitment to targeting specific molecular abnormalities and providing the right treatment to the right patient at the right time.”

XALKORI is an oral, anaplastic lymphoma kinase (ALK) inhibitor.[1] By inhibiting the ALK fusion protein, XALKORI blocks signaling in a number of cell pathways that are believed to be critical for the growth and survival of tumor cells, which may lead to growth inhibition or regression of tumors.[2,3]

About XALKORI (crizotinib)

XALKORI is a first-in-class medicine that has received conditional marketing authorization in Europe. XALKORI was first approved in the U.S. in August 2011 for the treatment of locally advanced or metastatic NSCLC that is ALK-positive as detected by a Food and Drug Administration (FDA)-approved test. This indication is based on response rate. There are no data available demonstrating improvements in patient-reported outcomes or survival with XALKORI. XALKORI also has received approval in a number of other countries, including Switzerland, Canada, South Korea and Japan. Additional applications are under regulatory review in several countries worldwide.

Important XALKORI(crizotinib)Safety Information4

Hepatotoxicity: Drug-induced hepatotoxicity with fatal outcome has occurred. Transaminase elevations generally occurred within the first 2 months of treatment. XALKORI should not be used in patients with severe hepatic impairment. Liver function tests including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin should be monitored twice a month during the first 2 months of treatment, then once a month and as clinically indicated, with more frequent repeat testing for Grades 2, 3, or 4 elevation. Temporarily suspend, dose reduce, or permanently discontinue XALKORI as indicated.

Pneumonitis: XALKORI has been associated with severe, life-threatening, or fatal treatment-related pneumonitis in clinical trials with a frequency of 4 in 386 (1%) patients. All of these cases occurred within 2 months after the initiation of treatment. Patients with pulmonary symptoms indicative of pneumonitis should be monitored. XALKORI treatment should be withheld if pneumonitis is suspected. Other causes of pneumonitis should be excluded and XALKORI should be permanently discontinued in patients diagnosed with treatment-related pneumonitis.

QT Interval Prolongation: QTc prolongation has been observed, which may lead to an increased risk for ventricular tachyarrhythmias (e.g. Torsades de Pointes) or sudden death. The risk of QTc prolongation may be increased in patients concomitantly taking antiarrhythmics and in patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances (e.g., secondary to diarrhea or vomiting). XALKORI should be administered with caution to patients who have a history of or predisposition for QTc prolongation, or who are taking medicinal products that are known to prolong the QT interval. When using XALKORI in these patients, periodic monitoring with electrocardiograms and electrolytes should be considered. Permanently discontinue XALKORI for grade 4 QTc prolongation. XALKORI should be withheld for grade 3 QTc prolongation until recovery to ? grade 1. Permanently discontinue XALKORI if grade 3 QTc prolongation recurs.

ALK Testing: An accurate and validated ALK assay is necessary for the selection of patients for treatment with XALKORI. Assessment for ALK-positive NSCLC should be performed by laboratories with demonstrated proficiency in the specific technology being utilized.

Pregnancy: XALKORI may cause fetal harm when administered to a pregnant woman. Studies in animals have shown reproductive toxicity. There are no data in pregnant women using XALKORI. This medicinal product should not be used during pregnancy unless the clinical condition of the mother requires treatment. Pregnant women, or patients becoming pregnant while receiving XALKORI, or treated male patients as partners of a pregnant women, should be apprised of the potential hazard to the fetus.

Adverse Reactions: Safety of XALKORI was evaluated in 386 patients with previously treated ALK-positive NSCLC in 2 single-arm clinical trials (Study 1001 and PROFILE 1005). The most common any-grade adverse reactions (>20%) across both studies were vision disorder, nausea, diarrhea, vomiting, edema, constipation, and fatigue. The most common Grade 3 or 4 adverse reactions (?3%) across both studies were increased ALT and neutropenia.

- Vision disorder including diplopia, photopsia, vision blurred, visual impairment, and vitreous floaters was experienced by 76 (61%) patients in Study 1001 and 149 (57%) patients in PROFILE 1005. Ophthalmological evaluation should be considered if vision disorder persists or worsens in severity.
- Nausea, diarrhea, vomiting, and constipation were the most commonly reported gastrointestinal events, and were primarily Grade 1 in severity. Supportive care for gastrointestinal events may include standard antiemetic and/or antidiarrheal or laxative medicinal products.
- Neuropathy, primarily peripheral neuropathy, was experienced by 11 (9%) patients in Study 1001 and 33 (13%) patients in PROFILE 1005, and was primarily Grade 1 in severity. Dizziness and dysgeusia were also very commonly reported in these studies, but were all Grades 1 or 2 in severity.

Drug Interactions: The concomitant use of XALKORI with strong CYP3A4 inhibitors/inducers and CYP3A4 substrates with narrow therapeutic indices should be avoided.

Breast-feeding: It is not known whether XALKORI and its metabolites are excreted in human milk. Because of the potential harm to the infant, mothers should be advised to avoid breast-feeding while receiving XALKORI.

Hepatic Impairment: XALKORI has not been studied in patients with hepatic impairment. Treatment with XALKORI should be used with caution in patients with mild and moderate hepatic impairment. XALKORI should not be used in patients with severe hepatic impairment.

Renal Impairment: No starting dose adjustment is recommended for patients with mild and moderate renal impairment. No data are available for patients with severe and end-stage renal disease. Therefore, no formal dosing recommendation can be made.

About Pfizer Oncology

Pfizer Oncology is committed to the discovery, investigation and development of innovative treatment options to improve the outlook for cancer patients worldwide. Our strong pipeline of biologics and small molecules, one of the most robust in the industry, is studied with precise focus on identifying and translating the best scientific breakthroughs into clinical application for patients across a wide range of cancers. By working collaboratively with academic institutions, individual researchers, cooperative research groups, governments, and licensing partners, Pfizer Oncology strives to cure or control cancer with breakthrough medicines, to deliver the right drug for each patient at the right time. For more information please visit www.Pfizer.com.

DISCLOSURE NOTICE: The information contained in this release is as of October 24, 2012. 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 that involves substantial risks and uncertainties about an oncology product, XALKORI. Such risks and uncertainties include, among other things, whether and when the European Commission (EC) will convert the conditional marketing authorization to a normal marketing authorization in the EU, as well as the EC's decisions regarding labeling and other matters that could affect XALKORI's availability or commercial potential in the EU; whether and when regulatory authorities in various other jurisdictions in which applications for XALKORI have been filed will approve such applications, as well as their decisions regarding labeling and other matters that could affect XALKORI's availability or commercial potential in such jurisdictions; 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, 2011 and in its reports on Form 10-Q and Form 8-K.

[1] Kwak E, Bang Y, Camidge R, et al. Anaplastic Lymphoma Kinase Inhibition in Non-Small Cell Lung Cancer. *N Engl J Med*. 2010;363:1693-1703.

[2] Chiarle R, Voena C, Ambrogio C, et al. The Anaplastic Lymphoma Kinase in the Pathogenesis of Cancer. *Nat Rev Cancer*. 2008;8(1):11-23.

[3] Zou HY, Li Q, Lee JH, et al. An Orally Available Small-Molecule Inhibitor of c-MET, PF-2341066, Exhibits Cytoreductive Antitumor Efficacy through Antiproliferative and Antiangiogenic Mechanisms. *Cancer Res.* 2007;67:4408-4417.

[4] XALKORI Summary of Product Characteristics (SmPC) for the European Union.

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