Pfizer Logo

Pfizer’s XALKORI® (crizotinib) Approved by FDA for ALK-positive Anaplastic Large Cell Lymphoma in Children and Young Adults

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XALKORI is the first biomarker-driven therapy for relapsed or refractory ALCL in young people

NEW YORK--(BUSINESS WIRE)-- Pfizer Inc. (NYSE:PFE) today announced that the U.S. Food and Drug Administration (FDA) approved the supplemental New Drug Application (sNDA) for XALKORI® (crizotinib) for the treatment of pediatric patients 1 year of age and older and young adults with relapsed or refractory, systemic anaplastic large cell lymphoma (ALCL) that is anaplastic lymphoma kinase (ALK)-positive. The safety and efficacy of XALKORI have not been established in older adults with relapsed or refractory, systemic ALK-positive ALCL. ALCL is a rare form of non-Hodgkin lymphoma (NHL) and accounts for approximately 30% of cases of NHL in young people.[1,2,3] Approximately 90% of ALCL cases in young people are ALK-positive.[4,5,6]

“We are proud to deliver the first biomarker-driven therapy for children and young adults with ALCL. XALKORI offers a meaningful new treatment option for young patients with relapsed or refractory ALK-positive ALCL,” said Chris Boshoff, M.D., Ph.D., Chief Development Officer, Oncology, Pfizer Global Product Development. “XALKORI transformed the treatment of ALK-positive non-small cell lung cancer as the first biomarker-driven therapy for that disease, and this approval is a notable milestone in our journey to continue to follow the science to address cancers with significant unmet need.”

Although the majority of people with ALK-positive ALCL respond well to chemotherapy and experience long-term remission, a number of patients will unfortunately relapse or require alternative treatment approaches.[7]

“With increased attention being placed on the development of targeted agents and the importance of ALK in pediatric patients with ALCL, the approval of XALKORI is a significant victory in our ongoing fight against these cancers that provides an outpatient oral medication with the real possibility of robust and sustained responses,” said Yael Mossé, M.D., Associate Professor of Pediatrics at the University of Pennsylvania/ Children’s Hospital of Philadelphia and Principal Investigator for the pivotal study run through the Children’s Oncology Group. “ALK fusions play an important role in the pathology of ALCL, and it’s exciting that XALKORI is able to leverage this dependence to provide a treatment option for young people faced with ALCL disease progression.”

The FDA approval is based on results from Study ADVL0912 (NCT00939770), a multicenter, single arm, open-label study in 121 patients between the ages of 1 and 21 that included 26 patients with relapsed or refractory, systemic ALK-positive ALCL after at least one systemic treatment. Treatment with XALKORI resulted in an objective response rate of 88%. Among the 23 patients who achieved a response, 39% maintained their response for at least 6 months and 22% maintained their response for at least 12 months.[8]

The safety profile of XALKORI in ALK-positive ALCL in children and young adults is generally consistent with that observed in patients with ALK-positive and ROS1-positive metastatic NSCLC. The most common adverse reactions (?35%), excluding laboratory abnormalities, were diarrhea, vomiting, nausea, vision disorder, headache, musculoskeletal pain, stomatitis, fatigue, decreased appetite, pyrexia, abdominal pain, cough and pruritis. The most common Grade 3 or 4 laboratory abnormalities (?15%) included neutropenia, lymphopenia and thrombocytopenia. Grade 4 laboratory abnormalities (?15%) included neutropenia (62%), lymphopenia (35%) and thrombocytopenia (19%). In Study ADVL0912, visual disorders occurred in 46% of 121 patients treated with XALKORI, including 65% of the 26 patients diagnosed with ALCL.[8]

“Crizotinib represents an exciting new development in the treatment of this disease,” said Meghan Gutierrez, Chief Executive Officer at the Lymphoma Research Foundation. “Researchers have made significant progress in our understanding of ALCL, which we hope will continue to improve treatment strategies and the options for children with ALCL. Today’s news builds upon this progress and provides hope to pediatric patients with ALCL and their loved ones.”

XALKORI received Breakthrough Therapy designation (BTD) from the FDA for the ALK-positive ALCL indication in May 2018. The European Medicines Agency (EMA) has agreed to a Paediatric Investigational Plan (PIP) for XALKORI including the treatment of pediatric patients with relapsed or refractory systemic ALK-positive ALCL. This agreement provides a path for a potential regulatory submission for XALKORI in pediatric patients with relapsed or refractory ALK-positive ALCL in the European Union.

About XALKORI® (crizotinib)

XALKORI is a tyrosine kinase inhibitor (TKI) indicated for the treatment of patients with metastatic NSCLC whose tumors are ALK- or ROS1-positive as detected by an FDA-approved test. In addition to the United States, 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 70 countries.

XALKORI is indicated for the treatment of pediatric patients 1 year of age and older and young adults with relapsed or refractory, systemic anaplastic large cell lymphoma (ALCL) that is ALK-positive. The safety and efficacy of XALKORI have not been established in older adults with relapsed or refractory, systemic ALK-positive ALCL.

The full prescribing information for XALKORI can be found here.

IMPORTANT XALKORI® (crizotinib) SAFETY INFORMATION FROM THE U.S. PRESCRIBING INFORMATION

IMPORTANT SAFETY INFORMATION FOR RELAPSED OR REFRACTORY, SYSTEMIC ALK-POSITIVE ANAPLASTIC LARGE CELL LYMPHOMA

Hepatotoxicity: In a study with 121 patients ages 1 to ?21 years treated with XALKORI for relapsed or refractory tumors including ALCL, 71% and 79% had increases of AST and ALT, respectively, with increased ALT or AST >5 times the ULN in 6% each. Of the 26 patients with ALCL treated with XALKORI, 65% and 81% had increases of AST and ALT, respectively, with increases >5 times the ULN in 4% each.

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 increased transaminases.

Withhold, reduce dose, or permanently discontinue XALKORI for hepatotoxicity as recommended

Interstitial Lung Disease/Pneumonitis: Among 121 patients ages 1 to ?21 years with relapsed or refractory tumors, including ALCL, ILD occurred in 0.8% of patients. Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis. Exclude other potential causes of ILD/pneumonitis, and permanently discontinue XALKORI in patients diagnosed with drug-related ILD/pneumonitis

QT Interval Prolongation: QTc prolongation was reported as an adverse reaction in 4.1% of patients, including 8% of patients with ALCL.

Avoid use of XALKORI 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 are known to prolong the QT interval. Withhold, reduce dose, or permanently discontinue XALKORI for QT/QTc interval prolongation as recommended.

Bradycardia: Symptomatic bradycardia can occur in patients receiving XALKORI. Among 121 patients ages 1 to ?21 years treated with XALKORI, bradycardia was reported in 14%, including Grade 3 bradycardia in 0.8% of patients. Of the 26 patients with ALCL treated with XALKORI, bradycardia (all Grade 1) was reported in 19%.

Avoid using XALKORI in combination with other medications known to cause bradycardia (e.g., beta-blockers, non?dihydropyridine calcium channel blockers, clonidine, and digoxin) to the extent possible. Monitor heart rate and blood pressure regularly. If bradycardia occurs, re-evaluate for the use of concomitant medications known to cause bradycardia. Withhold, reduce dose, or permanently discontinue XALKORI for bradycardia as recommended

Severe Visual Loss: Visual disorders occurred in 46% of 121 patients with XALKORI, including 65% of 26 patients with ALCL. Of the 56 patients who experienced visual disorders, one patient experienced Grade 3 optic nerve disorder. The most common visual symptoms were blurred vision and visual impairment.

For patients with ALCL, obtain baseline ophthalmologic examination prior to starting XALKORI. Follow-up ophthalmologic examination including retinal examination is recommended within 1 month of starting XALKORI, every 3 months thereafter, and upon any new visual symptoms. Assessment of visual symptoms is recommended monthly during treatment. Report any visual symptoms to an eye specialist. Monitor symptoms and report any visual symptoms (Grade 1 or 2) to an eye specialist. Consider dose reduction for Grade 2 visual disorders. Withhold XALKORI pending evaluation for any Grade 3 or 4 ocular disorders, and permanently discontinue XALKORI for Grade 3 of 4 ocular disorders unless another cause is identified. Discontinue XALKORI in any patient with new onset of severe visual loss (best corrected vision less than 20/200 in one or both eyes). Perform an ophthalmological evaluation consisting of best corrected visual acuity, retinal photographs, visual fields, optical coherence tomography (OCT) and other evaluations as appropriate for new onset of visual loss, and for other visual symptoms as clinically warranted.

There is insufficient information to characterize the risks of resumption of XALKORI in patients who develop visual symptoms or visual loss. A decision to resume XALKORI should consider the potential benefits versus risks to the patient.

Gastrointestinal Toxicity: XALKORI can cause severe gastrointestinal toxicities in patients with ALCL. In patients with ALCL (n=26), gastrointestinal toxicity occurred in 100% of patients; Grade 3 gastrointestinal toxicity occurred in 27% of patients and included diarrhea, nausea, vomiting, and stomatitis. Provide standard antiemetic and antidiarrheal agents for gastrointestinal toxicities in patients with ALCL. Antiemetics are

recommended prior to and during treatment with XALKORI to prevent nausea and vomiting. If patients develop Grade 3 nausea lasting 3 days or Grade 3 or 4 diarrhea or vomiting despite maximum medical therapy, withhold XALKORI until resolved, and then resume at the next lower dose level. Consider supportive care such as hydration, electrolyte supplementation, and nutritional support as clinically indicated.

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 to use effective contraception during treatment with XALKORI and for at least 45 days following the final dose. Advise males with female partners of reproductive potential to use condoms during treatment with XALKORI and for at least 90 days after the final dose.

Adverse Reactions: Safety was evaluated in a multicenter, single arm, open-label study in patients 1 to ?21 years of age that included 26 patients with relapsed or refractory, systemic ALK-positive ALCL after at least one systemic treatment. Serious adverse reactions occurred in 35% of patients treated with XALKORI. The most frequent serious adverse reactions were neutropenia (12%) and hypotension (8%). The most common adverse reactions (?35%), excluding laboratory abnormalities, were diarrhea, vomiting, nausea, vision disorder, headache, musculoskeletal pain, stomatitis, fatigue, decreased appetite, pyrexia, abdominal pain, cough, and pruritis. The most common Grade 3 or 4 laboratory abnormalities (?15%) included neutropenia, lymphopenia, and thrombocytopenia. Grade 4 laboratory abnormalities (?15%) included neutropenia (62%), lymphopenia (35%), and thrombocytopenia (19%).

Drug Interactions: Use caution with concomitant use with strong CYP3A inhibitors as these increase XALKORI plasma concentrations. If concomitant use of strong CYP3A inhibitors is unavoidable, reduce the dose of XALKORI to the second dose reduction based on BSA. After discontinuation of a strong CYP3A inhibitor, resume the XALKORI dose used prior to initiating the strong CYP3A inhibitor. Avoid grapefruit or grapefruit juice which may also increase plasma concentrations of XALKORI. Use caution with concomitant use of moderate CYP3A inhibitors. Concomitant use of XALKORI with strong CYP3A inducers decreases XALKORI plasma concentrations which may decrease the efficacy of XALKORI. Avoid concomitant use of strong CYP3A inducers as they decrease crizotinib plasma concentrations. Avoid concomitant use of CYP3A substrates where minimal concentration changes may lead to serious adverse reactions. If concomitant use of XALKORI is unavoidable, decrease the CYP3A substrate dosage in accordance with approved product labeling.

Pediatric Use: The safety and effectiveness of XALKORI have been established in pediatric patients 12 months of age and older with relapsed or refractory, systemic ALK-positive ALCL. The safety and effectiveness have not been established in pediatric patients younger than 12 months of age with ALCL or in any pediatric patients with NSCLC.

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

Hepatic Impairment: The recommended dose of XALKORI in patients with moderate hepatic impairment [any AST and total bilirubin >1.5 times the ULN ?3 times ULN] is the first dose reduction based on BSA. The recommended dose of XALKORI in patients with severe hepatic impairment (any AST and total bilirubin >3 times ULN) is the second dose reduction based on BSA.

Renal Impairment: The recommended dosage of XALKORI in patients with severe renal impairment (CL_{cr}) <30 mL/min, calculated using the modified Cockcroft-Gault equation for adult patients and the Schwartz equation for pediatric patients not requiring dialysis is the second dose reduction based on BSA.

IMPORTANT SAFETY INFORMATION FOR NSCLC

Hepatotoxicity: Drug-induced hepatotoxicity with fatal outcome occurred in 0.1% of patients treated with XALKORI across clinical trials (n=1719). Increased transaminases 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 increased transaminases. 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% of 1582 patients 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 baseline or a QTc ?481 ms, then resume at next lower dosage.

Bradycardia: Symptomatic bradycardia can occur. Across clinical trials, bradycardia occurred in 13% of patients treated with XALKORI (n=1719). Avoid use in combination with other medications known to cause bradycardia. Monitor heart rate and blood pressure regularly. If bradycardia occurs, re-evaluate for the use of concomitant medications known to cause bradycardia. 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 visual loss was 0.2% of 1719 patients. Optic atrophy and optic nerve disorder have been reported as potential causes of visual loss. Monitor symptoms and report any symptoms to an eye specialist. 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% 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%), neuropathy (21%), and rash (11%) also occurred in patients taking XALKORI.

Drug Interactions: Avoid concomitant use of XALKORI with strong CYP3A inhibitors as these increase XALKORI plasma concentrations. Avoid grapefruit or grapefruit juice which may also increase plasma concentrations of XALKORI. Use caution with concomitant use of moderate CYP3A inhibitors. Concomitant use of XALKORI with strong CYP3A inducers decreases XALKORI plasma concentrations which may decrease the efficacy of XALKORI. Avoid concomitant use of strong CYP3A inducers. Concomitant use of XALKORI increases plasma concentrations of CYP3A substrates. Avoid concomitant use of XALKORI with CYP3A substrates where minimal concentration changes may lead to serious adverse reactions. If concomitant use of XALKORI is unavoidable, decrease the CYP3A substrate dosage in accordance with approved product labeling.

Lactation: Because of the potential for adverse reactions in breastfed children, advise women 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 dosage 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.

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 January 14, 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 XALKORI® (crizotinib) and a new indication in the U.S. for the treatment of pediatric patients 1 year of age and older and young adults with relapsed or refractory, systemic anaplastic large cell lymphoma (ALCL) that is anaplastic lymphoma kinase (ALK)-positive, 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 XALKORI; 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 XALKORI for the new indication (including in the European Union) or in any jurisdictions for any other potential indications for XALKORI; whether and when any such other applications may be approved by regulatory authorities, 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 XALKORI; 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, 2019 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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