

<b>PRODUCT DESCRIPTION</b>	<p>XALKORI® is an oral first-in-class medicine that inhibits the anaplastic lymphoma kinase (ALK).<sup>1</sup></p>
<b>LICENSING STATUS</b>	<p>In March 2012, XALKORI was approved for the treatment of patients with previously treated ALK-positive advanced NSCLC in Switzerland by the Swiss Agency for Therapeutic Products.</p> <p>In August 2011, XALKORI was first approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with locally advanced or metastatic NSCLC that is ALK-positive as detected by an FDA-approved test.</p> <p>XALKORI is also approved in other countries across North and South America and in Asia with additional marketing applications under review.</p>
<b>MECHANISM OF ACTION</b>	<p>Originally discovered as an oncogenic driver in a subtype of lymphoma, ALK gene alterations are also believed to play a key role in tumor development in a subgroup of NSCLC and rare sarcomas. In ALK-positive lung cancer, a normally dormant gene, “ALK” is fused with another gene, predominantly “EML4”. This genetic alteration creates the ALK fusion gene and ultimately, production of ALK fusion protein, which is responsible for tumor growth.<sup>2</sup></p> <p>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. XALKORI has also demonstrated inhibition of other receptor tyrosine kinases, some of which are being investigated.<sup>2,3</sup></p>
<b>NSCLC CLINICAL STUDIES</b>	<p>XALKORI was studied in patients with locally advanced or metastatic ALK-positive NSCLC across two multi-center, single-arm studies, including a Phase 2 study (PROFILE 1005) and an expansion cohort of a Phase 1 study (Study 1001).<sup>4</sup></p> <ul style="list-style-type: none"> <li>○ The primary endpoints in both studies were Objective Response Rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST), safety and tolerability.</li> <li>○ Secondary endpoints included Time to Tumor Response (TTR), Duration of Response (DR), Disease Control Rate (DCR), Progression-Free Survival (PFS), and Overall Survival (OS).</li> </ul> <ul style="list-style-type: none"> <li>• PROFILE 1005 evaluated 261 patients for tumor response.<sup>4</sup> <ul style="list-style-type: none"> <li>○ ALK-positive NSCLC tumors were identified using the Vysis ALK Break-Apart FISH Probe Kit assay.</li> </ul> </li> <li>• Study 1001 included 125 patients with previously treated ALK-positive advanced NSCLC.<sup>4</sup> <ul style="list-style-type: none"> <li>○ ALK-positive NSCLC was identified using a number of local clinical trial assays.</li> </ul> </li> </ul>
<b>EFFICACY</b>	<ul style="list-style-type: none"> <li>• In PROFILE 1005 (n=261), XALKORI achieved an ORR of 53 percent (95 percent CI, 47 percent, 60 percent).<sup>4</sup> <ul style="list-style-type: none"> <li>○ Eighty-five percent of disease control rates were achieved during the first six weeks of treatment.</li> <li>○ The median response duration was 43 weeks (95 percent CI, 36 weeks, 50 weeks).</li> </ul> </li> <li>• In Study 1001 (n=125), XALKORI achieved an ORR of 60 percent (95 percent CI: 51 percent, 69 percent).<sup>4</sup> <ul style="list-style-type: none"> <li>○ The median response duration was 48 weeks (95 percent CI, 36 weeks, 64 weeks).</li> </ul> </li> </ul>

<p><b>SAFETY PROFILE</b></p>	<p><b>IMPORTANT SAFETY INFORMATION</b></p> <p><b>Hepatotoxicity:</b> 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 ALT, 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.</p> <p><b>Pneumonitis:</b> 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.</p> <p><b>QT Interval Prolongation:</b> 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 <math>\leq</math> grade 1. Permanently discontinue XALKORI if grade 3 QTc prolongation recurs.</p> <p><b>ALK Testing:</b> 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.</p> <p><b>Pregnancy:</b> 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 crizotinib. 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 crizotinib, or treated male patients as partners of a pregnant women, should be apprised of the potential hazard to the fetus.</p> <p><b>Adverse Reactions:</b> 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 (&gt;20%) across both studies were vision disorder, nausea, diarrhea, vomiting, edema, constipation, and fatigue. The most common Grade 3 or 4 adverse reactions (<math>\geq</math>3%) across both studies were increased ALT and neutropenia.</p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• 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.</li> <li>• 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.</li> </ul>
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	<p>Dizziness and dysgeusia were also very commonly reported in these studies, but were all Grades 1 or 2 in severity.</p> <p><b>Drug Interactions:</b> The concomitant use of crizotinib with strong CYP3A4 inhibitors/inducers and CYP3A4 substrates with narrow therapeutic indices should be avoided.</p> <p><b>Breast-feeding:</b> It is not known whether crizotinib 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.</p> <p><b>Hepatic Impairment:</b> 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.</p> <p><b>Renal Impairment:</b> 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.</p>
<p><b>PATIENT ACCESS TO XALKORI</b></p>	<p>Pfizer is committed to helping eligible patients prescribed XALKORI gain access to the medication. Programs to facilitate this process will vary from country to country.</p>
<p><b>CONTACT &amp; ADDITIONAL INFORMATION</b></p>	<p><b>Pfizer Europe contact</b>  Matti Ojanen  Director, Pfizer EU Communications  Tel: (+44) 1737 332312  Mob: (+44) 7557 202394  <a href="mailto:matti.ojanen@pfizer.com">matti.ojanen@pfizer.com</a></p> <p>For more information about Xalkori trials, please visit <a href="http://www.clinicaltrials.gov">www.clinicaltrials.gov</a> or <a href="http://www.pfizercancertrials.com">www.pfizercancertrials.com</a>.</p>

<sup>1</sup>Kwak E, et al. Anaplastic Lymphoma Kinase Inhibition in Non-Small Cell Lung Cancer. *N Engl J Med*. October 28, 2010.

<sup>2</sup> 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.

<sup>3</sup> Zou HY, Li Q, Lee JH, et al. An Orally Available Small-Molecule Inhibitor of c-MET,

PF-2341066, Exhibits Cyto-reductive Antitumor Efficacy Through Antiproliferative and Antiangiogenic Mechanisms. *Cancer Res*. 2007;67:4408-4417.

<sup>4</sup> XALKORI Draft Summary of Product Characteristics (SmPC) for the European Union.