XALKORI® (crizotinib) 250 mg capsules is an oral medicine that inhibits the anaplastic lymphoma kinase (ALK) and ROS1 receptor tyrosine kinases.\(^1,2\)

XALKORI was the first ALK inhibitor approved in the U.S. and is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are ALK-positive as detected by an FDA-approved test.\(^3\)

XALKORI is also the first and only FDA-approved biomarker-driven therapy indicated for the treatment of patients with metastatic NSCLC whose tumors are ROS1-positive.

To date, over 8,000 patients have been treated with XALKORI in the U.S.\(^3\)

**ALK IN LUNG CANCER**

Originally discovered as an oncogenic driver in a type of lymphoma, ALK gene alterations were also found to be among key drivers of tumor development in cancers such as NSCLC and rare sarcomas.\(^4\) By inhibiting ALK, XALKORI blocks signaling in a number of cell pathways that are believed to be critical for the growth and survival of tumor cells.\(^4,5\)

In ALK-positive lung cancer, a normally dormant gene named ALK is fused with another gene, predominantly EML4. This genetic alteration creates the ALK fusion gene and ultimately, the production of the ALK fusion protein, which is responsible for tumor growth.\(^4,5\) Epidemiology studies suggest that approximately 3 to 5 percent of NSCLC tumors are ALK-positive.\(^6\)

Only biomarker testing can determine which patients have ALK-positive metastatic NSCLC. In the U.S., the Vysis ALK Break Apart FISH Probe Kit (Abbott Molecular) and the Ventana ALK (D5F3) CDx Assay are the only FDA-approved tests for detecting ALK.

**ROS1 IN LUNG CANCER**

Another gene that can rearrange or combine with other genes is called ROS1. Sometimes the ROS1 gene can attach to another gene, changing the way each gene normally functions. This ROS1 gene rearrangement can contribute to cancer-cell growth and tumor survival. This change occurs in approximately one percent of NSCLC cases. Of the estimated 1.5 million new cases of NSCLC worldwide each year, roughly 15,000 may be driven by oncogenic ROS1 fusions.\(^7,8,9\)

An FDA-approved test for the detection of ROS1 rearrangements in NSCLC is not currently available; however, laboratory developed tests are available. A companion diagnostic test is currently under development to identify patients with ROS1-positive metastatic NSCLC who may benefit from treatment with XALKORI.

**NSCLC CLINICAL STUDIES**

PROFILE 1014 studied XALKORI 250 mg twice daily in previously untreated patients with ALK-positive metastatic NSCLC versus standard platinum-based chemotherapy regimens. This Phase 3 study enrolled 343 participants from clinical sites globally.\(^10\) Patients in the chemotherapy arm of the study received one of the following standard-of-care chemotherapy regimens based on the choice of the investigator: either pemetrexed 500 mg/m\(^2\) with cisplatin 75 mg/m\(^2\) or carboplatin AUC of 5 or 6 min/mL by intravenous infusion every 3 weeks for up to 6 cycles. Patients were required to have ALK-positive NSCLC, as identified by the FDA-approved assay Vysis ALK Break Apart FISH Probe Kit, prior to randomization.

- In PROFILE 1014, XALKORI demonstrated significantly prolonged progression-free survival (PFS) of 10.9 months (95% CI, 8.3 to 13.9) (n=172) compared to 7.0 months (95% CI, 6.8 to 8.2) with chemotherapy (n=171) in previously untreated patients with ALK-positive metastatic NSCLC (hazard ratio, 0.45; 95% CI: 0.35 to 0.60; \(P<0.001\)).
- XALKORI also demonstrated significantly higher objective response rate (ORR) when compared to standard platinum-based chemotherapy regimens. XALKORI demonstrated an ORR of 74% (95% CI, 67 to 81) compared to an ORR of 45% (95% CI, 37 to 53) for the chemotherapy arm (\(P<0.001\)).
NSCLC CLINICAL STUDIES (CONTINUED)

• Median duration of response was 11.3 months (95% CI, 8.1 to 13.8) with XALKORI and 5.3 months (95% CI, 4.1 to 5.8) with chemotherapy.

• With the majority of patients still in follow up for survival at the time of the PFS analysis, and over two-thirds of the patients randomized to the chemotherapy arm of the study subsequently crossing over to XALKORI, median OS was not reached in either treatment arm (hazard ratio, 0.82; 95% CI, 0.54 to 1.26; \(P=0.36\)). The OS analysis conducted at the time of the PFS analysis did not suggest a difference in survival between arms.

• Safety data for PROFILE 1014 is based on 340 patients (including n=171 in the XALKORI arm and n=169 in the chemotherapy arm). Serious adverse events were reported in 58 patients (34%) treated with XALKORI:
  – The most frequent serious adverse events reported in patients treated with XALKORI were dyspnea (4.1%) and pulmonary embolism (2.9%).
  – Fatal adverse events in XALKORI-treated patients occurred in 2.3% 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%), 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%) and neuropathy (21%) also occurred in patients taking XALKORI.

STUDY 1001 is a multicenter, single-arm Phase 1 study that included a cohort of 50 patients with ROS1-positive metastatic NSCLC treated with 250 mg of XALKORI orally twice daily. In the clinical trial, tumors were tested for ROS1 rearrangement by laboratory-developed break-apart fluorescence in situ hybridization (FISH) (96%) or RT-PCR (4%) clinical trial assays.

• The efficacy outcome measures were objective response rate (ORR) and duration of response as assessed by independent radiology review (IRR) and investigator.
  – The ORR was 66% (95% CI, 51 to 79) as assessed by IRR. There was one complete response and 32 partial responses.
  – The median duration of response as assessed by IRR was 18.3 months (95% CI, 12.7 months, not reached).

• Additionally, the safety profile of XALKORI in ROS1-positive metastatic NSCLC was generally consistent with that observed 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.

SAFETY PROFILE

IMPORTANT SAFETY INFORMATION (CONTINUES ON NEXT PAGE)

Hepatotoxicity: Drug-induced hepatotoxicity with fatal outcome occurred in 0.1% of patients treated with XALKORI across clinical trials (n=1719). Transaminase elevations 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 transaminase elevations. 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.
SAFETY PROFILE (CONTINUED)

IMPORTANT SAFETY INFORMATION (CONTINUED)

Intersitial 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 5.0% 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 a QTc ≤480 ms, then resume at a reduced dose.

Bradycardia: Symptomatic bradycardia can occur. Across clinical trials, bradycardia occurred in 12.7% of patients treated with XALKORI (n=1719). Avoid use in combination with other agents known to cause bradycardia. Monitor heart rate and blood pressure regularly. In cases of symptomatic bradycardia that is not life-threatening, hold XALKORI until recovery to asymptomatic bradycardia or to a heart rate of ≥60 bpm, re-evaluate the use of concomitant medications, and adjust the dose of 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 vision loss was 0.2% (n=1719). 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 63.1% 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 4 vision disorders in patients taking XALKORI.

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 (41.1%) and pulmonary embolism (29.2%). 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 12%), 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 4/5 reactions occurring at a ≥2% higher incidence with XALKORI vs chemotherapy were QT prolongation (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%), and neuropathy (21%) also occurred in patients taking XALKORI.

Continues on next page
SAFETY PROFILE (CONTINUED)

IMPORTANT SAFETY INFORMATION (CONTINUED)

Drug Interactions: Exercise caution with concomitant use of moderate CYP3A inhibitors. Avoid grapefruit or grapefruit juice which may increase plasma concentrations of crizotinib. Avoid concomitant use of strong CYP3A inducers and inhibitors. Avoid concomitant use of CYP3A substrates with narrow therapeutic range in patients taking XALKORI. If concomitant use of CYP3A substrates with narrow therapeutic range is required in patients taking XALKORI, dose reductions of the CYP3A substrates may be required due to adverse reactions.

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

Hepatic Impairment: XALKORI has not been studied in patients with hepatic impairment. As crizotinib is extensively metabolized in the liver, hepatic impairment is likely to increase plasma crizotinib concentrations. Use caution in patients with hepatic impairment.

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. No starting dose adjustment is needed for patients with mild and moderate renal impairment.

Please see full Prescribing Information for XALKORI.

For more information about XALKORI please visit www.XALKORI.com.

CONTACT & ADDITIONAL INFORMATION

Pfizer Media Relations Contact
Sally Beatty – Pfizer Oncology Media Relations
Sally.Beatty@pfizer.com
Phone: 212-733-6566
Mobile: 347-330-7867

For more information about XALKORI trials currently ongoing and enrolling, please visit www.clinicaltrials.gov or www.pfizercancertrials.com.

REFERENCES


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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use XALKORI® safely and effectively. See full prescribing information for XALKORI.

XALKORI® (crizotinib) capsules, for oral use

Initial U.S. Approval: 2011

RECENT MAJOR CHANGES

Indications and Usage, ROS1-Positive Metastatic NSCLC (1.2) Dosage and Administration, Patient Selection (2.1) Warnings and Precautions, Severe Visual Loss (5.5) Warnings and Precautions, Embryo-Fetal Toxicity (5.6)

3/2016
3/2016
9/2015
3/2016

INDICATIONS AND USAGE
XALKORI is a kinase inhibitor indicated for the treatment of patients with:
• metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test. (1.1)
• metastatic NSCLC whose tumors are ROS1-positive. (1.2)

DOSE AND ADMINISTRATION

Recommended Dose: 250 mg orally, twice daily. (2.2)

Treatment of Patients with Severe Renal Impairment

A reduced dose of XALKORI (250 mg orally once daily) is recommended for patients with severe renal impairment (creatinine clearance <30 mL/min) not requiring dialysis. (2.2)

Dosage Forms and Strengths

Capsules: 250 mg and 200 mg. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

Hepatotoxicity: Fatal hepatotoxicity occurred in 0.1% of patients. Monitor with periodic liver testing. Temporarily suspend, dose reduce, or permanently discontinue XALKORI. (5.1)

Adverse Reactions

The most common adverse reactions (≥25%) are vision disorders, nausea, diarrhea, vomiting, edema, constipation, elevated transaminases, fatigue, decreased appetite, upper respiratory tract infection, dizziness, and neuropathy. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc. at 1-800-FDA-1088 or www.fda.gov/medwatch.

FULL PRESCRIBING INFORMATION: CONTENTS*

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1.1 ALK-Positive Metastatic NSCLC
1.2 ROS1-Positive Metastatic NSCLC

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2.1 Patient Selection
2.2 Recommended Dosing
2.3 Dose Modification

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS
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5.2 Interstitial Lung Disease (Pneumonitis)
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16 HOW SUPPLIED/STORAGE AND HANDLING

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* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 ALK-Positive Metastatic NSCLC

XALKORI is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test. [see Clinical Studies (14.1)].

1.2 ROS1-Positive Metastatic NSCLC

XALKORI is indicated for the treatment of patients with metastatic NSCLC whose tumors are ROS1-positive [see Clinical Studies (14.2)].

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for the treatment of metastatic NSCLC with XALKORI based on the presence of ALK rearrangements determined by local laboratory methods. (1.1)

2.2 Recommended Dosing

The recommended dose of XALKORI in patients with severe renal impairment (creatinine clearance <30 mL/min) not requiring dialysis is 250 mg orally once daily. (2.2)

2.3 Dose Modification

Reduce dose as below, if 1 or more dose reductions are necessary due to adverse reactions of Grade 3 or 4 severity, as defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0:
• First dose reduction: XALKORI 200 mg taken orally twice daily
• Second dose reduction: XALKORI 150 mg taken orally twice daily
• Permanently discontinue if unable to tolerate XALKORI 250 mg taken orally once daily

Dose reduction guidelines are provided in Tables 1 and 2.

Table 1. XALKORI Dose Modification – Hematologic Toxicities*

<table>
<thead>
<tr>
<th>Grade</th>
<th>XALKORI Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3</td>
<td>Withhold until recovery to Grade 2 or less, then resume at the same dose schedule</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Withhold until recovery to Grade 2 or less, then resume at next lower dose</td>
</tr>
</tbody>
</table>

* Except lymphopenia (unless associated with clinical events, e.g., opportunistic infections).

Table 2. XALKORI Dose Modification – Non-Hematologic Toxicities

<table>
<thead>
<tr>
<th>Criteria</th>
<th>XALKORI Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>Withhold until recovery to baseline or less than or equal to 3 times ULN, then resume at reduced dose.</td>
</tr>
<tr>
<td>ALT or AST elevation greater than 3 times ULN with concurrent total bilirubin elevation greater than 1.5 times ULN (in the absence of cholestasis or hemolysis)</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td>Any grade drug-related interstitial lung disease/pneumonitis</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td>QT corrected for heart rate (QTC) greater than 500 ms on at least 2 separate electrocardiograms (ECGs)</td>
<td>Withhold until recovery to baseline or to a QTC less than 481 ms, then resume at reduced dose.</td>
</tr>
<tr>
<td>QTC greater than 500 ms or greater than or equal to 50 ms change from baseline with Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia</td>
<td>Permanently discontinue.</td>
</tr>
</tbody>
</table>
Table 2. XALKORI Dose Modification – Non-Hematologic Toxicities (cont’d)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>XALKORI Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradycardia= (symptomatic, may be severe and medically significant, medical intervention indicated)</td>
<td>Withhold until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. Evaluate concomitant medications known to cause bradycardia, as well as antiarrhythmic medications. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at previous dose upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, resume at reduced dose upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above.</td>
</tr>
<tr>
<td>Bradycardia= (life-threatening consequences, urgent intervention indicated)</td>
<td>Permanently discontinue if no contributing concomitant medication is identified. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at 250 mg once daily upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring.</td>
</tr>
<tr>
<td>Visual Loss (Grade 4 Ocular Disorder)</td>
<td>Discontinue during evaluation of severe vision loss.</td>
</tr>
</tbody>
</table>

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1 Heart rate less than 60 beats per minute (bpm).
2 Permanently discontinue for recurrence.

Monitor complete blood counts including differential white blood cell counts monthly and as clinically indicated, with more frequent repeat testing if Grade 3 or 4 abnormalities are observed, or if fever or infection occurs.

3 DOSE FORMS AND STRENGTHS
- 250 mg capsules: hard gelatin capsule, size 0, pink opaque cap and body, with “Pfizer” on the cap and “CRZ 250” on the body.
- 200 mg capsules: hard gelatin capsule, size 1, white opaque body and pink opaque cap, with “Pfizer” on the cap and “CRZ 200” on the body.

4 CONTRAINDICATIONS
- None.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity
Drug-induced hepatotoxicity with fatal outcome occurred in 2 (0.1%) of the 1719 patients treated with XALKORI across clinical trials. Concurrent elevations in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than or equal to 3 times the upper limit of normal (ULN) and total bilirubin greater than or equal to 2 times the ULN, with normal alkaline phosphatase, occurred in 10 patients (<1%) treated with XALKORI. Elevations in ALT or AST greater than 5 times the ULN occurred in 187 (11.2%) and 95 (5.7%) patients, respectively. Seventeen patients (1.0%) required permanent discontinuation due to elevated transaminases. Transaminase elevations generally occurred within the first 2 months of treatment.

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 transaminase elevations. Temporarily suspend, dose reduce, or permanently discontinue XALKORI as described in Table 2 [see Dosage and Administration (2.3) and Adverse Reactions (6)].

5.2 Interstitial Lung Disease (Pneumonitis)
Severe, life-threatening, or fatal interstitial lung disease (ILD)/pneumonitis can occur in patients treated with XALKORI. Across clinical trials (n=1719), 50 XALKORI-treated patients (2.9%) had ILD/pneumonitis. The incidence of Grade 4 ILD/pneumonitis in patients treated with XALKORI was 0.6% of 1719 patients. Across clinical trials, 434 patients with ALK-positive metastatic NSCLC who received XALKORI 250 mg twice daily enrolled on Studies 1 (including an additional 109 patients who crossed over from the control arm) and 2. 3. A single arm trial (n=1083) of ALK-positive NSCLC, and an additional ALK-positive NSCLC expansion cohort of a dose finding study (n=154) [see Warnings and Precautions (5)].

The data described below is based primarily on 343 patients with ALK-positive metastatic NSCLC who received XALKORI 250 mg twice daily from 2 open-label, randomized, active-controlled trials (Studies 1 and 2). The safety of XALKORI was also evaluated in 50 patients with ROS1-positive metastatic NSCLC from a single-patient cohort, dose-escalation and dose-expansion trials described below.

The most common adverse reactions (≥25%) of XALKORI are vision disorders, nausea, diarrhea, vomiting, edema, constipation, elevated transaminases, fatigue, decreased appetite, upper respiratory infection, dizziness, and neuropathy.

Previously Untreated ALK-Positive Metastatic NSCLC - Study 1
The data in Table 3 are derived from 340 patients with ALK-positive metastatic NSCLC who had not received previous systemic treatment for advanced disease. The median duration of treatment was 10.9 months for patients in the XALKORI arm and 4.1 months for patients in the chemotherapy arm. Median duration of treatment was 5.2 months for patients who received XALKORI after cross over from chemotherapy. Across the 340 patients who were treated in Study 1, the median age was 53 years; 16% of patients were older than 65 years. A total of 52% of patients were female and 45% were Asian.

Serious adverse events were reported in 58 patients (34%) treated with XALKORI. The most frequent serious adverse events reported in patients treated with XALKORI were dyspnea (4.1%) and pulmonary embolism (2.9%). Fatal adverse events in XALKORI-treated patients occurred in 2.3% patients, consisting of septic shock, acute respiratory failure, and diabetic ketoacidosis.

Dose reductions due to adverse reactions were required in 6.4% of XALKORI-treated patients. The most frequent adverse reactions that led to dose reduction in these patients were nausea (1.8%) and elevated transaminases (1.8%).

Permanent discontinuation of XALKORI treatment for adverse reactions was 2.8%. The most frequent adverse reactions that led to permanent discontinuation in XALKORI-treated patients were elevations transaminases (1.2%), hepatotoxicity (1.2%), and ILD (1.2%).

Tables 3 and 4 summarize common adverse reactions and laboratory abnormalities in XALKORI-treated patients.

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6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:
- Hepatotoxicity [see Warnings and Precautions (5.1)]
- Interstitial Lung Disease (Pneumonitis) [see Warnings and Precautions (5.2)]
- QT Interval Prolongation [see Warnings and Precautions (5.3)]
- Bradycardia [see Warnings and Precautions (5.4)]
- Severe Visual Loss [see Warnings and Precautions (5.5)]

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data in the Warnings and Precautions section reflect exposure to XALKORI in 1719 patients who received XALKORI 250 mg twice daily enrolled on Studies 1 (including an additional 109 patients who crossed over from the control arm) and 2. 3. A single arm trial (n=1083) of ALK-positive NSCLC, and an additional ALK-positive NSCLC expansion cohort of a dose finding study (n=154) [see Warnings and Precautions (5)].

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Serious adverse events were reported in 58 patients (34%) treated with XALKORI. The most frequent serious adverse events reported in patients treated with XALKORI were dyspnea (4.1%) and pulmonary embolism (2.9%). Fatal adverse events in XALKORI-treated patients occurred in 2.3% patients, consisting of septic shock, acute respiratory failure, and diabetic ketoacidosis.

Dose reductions due to adverse reactions were required in 6.4% of XALKORI-treated patients. The most frequent adverse reactions that led to dose reduction in these patients were nausea (1.8%) and elevated transaminases (1.8%).

Permanent discontinuation of XALKORI treatment for adverse reactions was 2.8%. The most frequent adverse reactions that led to permanent discontinuation in XALKORI-treated patients were elevations transaminases (1.2%), hepatotoxicity (1.2%), and ILD (1.2%).

Tables 3 and 4 summarize common adverse reactions and laboratory abnormalities in XALKORI-treated patients.
XALKORI was discontinued for adverse reactions in 15% of patients. The most frequent adverse reactions that led to discontinuation of XALKORI were ILD (1.7%), ALT and AST elevation (1.2%), dyspnea (1.2%), and pulmonary embolism (1.2%).

Tables 5 and 6 summarize common adverse reactions and laboratory abnormalities in XALKORI-treated patients.

### Table 3. Adverse Reactions Reported at a Higher Incidence (≥5% Higher for All Grades or ≥2% Higher for Grades 3-4) with XALKORI than Chemotherapy in Study 1

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>XALKORI (N=171)</th>
<th>Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) (N=169)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrocardiogram QT prolonged Bradycardia</td>
<td>6 (4%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vision disorder</td>
<td>71 (41%)</td>
<td>10 (6%)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>46 (27%)</td>
<td>36 (21%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>61 (36%)</td>
<td>13 (8%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>43 (25%)</td>
<td>30 (18%)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>14 (8%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>26 (15%)</td>
<td>12 (7%)</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>18 (10%)</td>
<td>10 (6%)</td>
</tr>
<tr>
<td>Headache</td>
<td>22 (13%)</td>
<td>15 (9%)</td>
</tr>
<tr>
<td>Laboratory Abnormality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>52 (31%)</td>
<td>11 (6%)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>48 (28%)</td>
<td>7 (4%)</td>
</tr>
<tr>
<td>ALT elevation</td>
<td>79 (46%)</td>
<td>15 (9%)</td>
</tr>
<tr>
<td>AST elevation</td>
<td>66 (39%)</td>
<td>8 (5%)</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>32 (19%)</td>
<td>10 (6%)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>49 (29%)</td>
<td>12 (7%)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>51 (30%)</td>
<td>9 (5%)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT elevation</td>
<td>76 (45%)</td>
<td>17 (10%)</td>
</tr>
<tr>
<td>AST elevation</td>
<td>61 (36%)</td>
<td>9 (5%)</td>
</tr>
</tbody>
</table>

### Table 4. Laboratory Abnormalities with Grade 3 or 4 Incidence of ≥4% in XALKORI-Treated Patients in Study 1

### Table 5. Adverse Reactions Reported at a Higher Incidence (≥5% Higher for All Grades or ≥2% Higher for Grades 3-4) with XALKORI than Chemotherapy in Study 2

### Table 6. Laboratory Abnormalities with Grade 3 or 4 Incidence of ≥4% in XALKORI-Treated Patients in Study 2

### Table 7. Laboratory Abnormalities with Grade 3 or 4 Incidence of ≥4% in XALKORI-Treated Patients in Study 3

### Table 8. Laboratory Abnormalities with Grade 3 or 4 Incidence of ≥4% in XALKORI-Treated Patients in Study 4

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*Adverse reactions were graded using NCI CTCAE version 4.0.*

*Includes cases reported within the clustered terms.*

*Bradycardia (Bradycardia, Sinus bradycardia).*

*Vision Disorder (Diplopia, Photophobia, Photopsia, Reduced visual acuity, Blurred vision, Vitreous floaters, Visual impairment).*

*Abdominal pain (Abdominal discomfort, Abdominal pain, Lower abdominal pain, Upper abdominal pain, Abdominal tenderness).*

*Edema (Edema, Peripheral edema, Face edema, Generalized edema, Local swelling, Periorbital edema).*

*Upper respiratory infection (Nasopharyngitis, Pharyngitis, Rhinitis, Upper respiratory tract infection).*

*Dizziness (Balance disorder, Dizziness, Postural dizziness, Presyncope).*

### Additional adverse reactions:

- **Cardiac Disorders:**
  - Electrocardiogram QT prolonged Bradycardia (6%), Diarrhea (6%), Constipation (4%), Dyspepsia (2%), Abdominal pain (2%), Vision disorder (1%).

- **Gastrointestinal Disorders:**
  - Vomiting (27%), Diarrhea (26%), Constipation (13%), Dyspepsia (10%), Abdominal pain (9%), Vision disorder (6%).

- **Nervous System Disorders:**
  - Dizziness (10%), Headache (13%).

- **Infections and Infestations:**
  - Upper respiratory infection (7%).

- **Musculoskeletal and Connective Tissue Disorders:**
  - Pain in extremity (7%), Muscle spasm (2%).

- **Laboratory Abnormalities:**
  - Hematology: Neutropenia (31%), Lymphopenia (28%).
  - Chemistry: ALT elevation (46%), AST elevation (39%), Hypophosphatemia (19%).

- **Laboratory Abnormality:**
  - ALT elevation (45%), AST elevation (36%), Hypophosphatemia (19%).

- **Chemistry:**
  - ALT elevation (45%), AST elevation (36%).

- **Laboratory Abnormality:**
  - ALT elevation (45%), AST elevation (36%).

- **Laboratory Abnormality:**
  - ALT elevation (45%), AST elevation (36%).

- **Laboratory Abnormality:**
  - ALT elevation (45%), AST elevation (36%).

- **Laboratory Abnormality:**
  - ALT elevation (45%), AST elevation (36%).
Neuropathy
No adverse effects were observed in animals and in Phase I, II, and III clinical trials. Neuropathy was observed in 2% of patients in clinical trials. Neuropathy has been reported in clinical trials of 20% of patients treated with XALKORI. Neuropathy is the most common adverse effect of XALKORI and is most often mild to moderate in severity. The most common types of neuropathy observed in clinical trials were sensory neuropathy and peripheral neuropathy.

Renal cysts were the most common adverse effect of XALKORI and were observed in 45% of patients in clinical trials. Renal cysts were experienced by 52 (3%) of 1719 patients. Renal cysts were experienced in some cases when imaging characteristics suggested an increased risk of malignancy. However, across clinical trials no renal accessions were confirmed by microbiology tests.

Renal impairment
The estimated glomerular filtration rate (eGFR) decreased from a baseline median of 94.62 mL/min/1.73 m² to a median of 50.23 mL/min/1.73 m² at 2 weeks (n=1499) in patients with ALK-positive advanced NSCLC who received XALKORI in clinical trials. No clinically relevant changes occurred in eGFR from 12 to 104 weeks of treatment. Median eGFR slightly increased (83.02 mL/min/1.73 m²) 4 weeks after the last dose of XALKORI. Overall, 76% of patients had a decrease in eGFR to <30 mL/min/1.73 m², 38% had a decrease to eGFR to <60 mL/min/1.73 m², and 3.6% had a decrease to eGFR to <30 mL/min/1.73 m².

8.7 Pregnancy
Risk Summary
Based on its mechanism of action, XALKORI can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1)]. There are no available data on the use of XALKORI during pregnancy. In animal reproduction studies, oral administration of crizotinib in pregnant rats during organogenesis at exposures similar to those expected with the maximum recommended human dose resulted in embryotoxicity and fetotoxicity [see Data]. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.8 Lactation
Risk Summary
There is no information regarding the presence of crizotinib in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for adverse reactions in breastfed infants, do not breastfeed during treatment with XALKORI and for 45 days after the final dose.

8.9 Females and Males of Reproductive Potential

8.9.1 Contraception
Females
XALKORI can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)]. Advise females of reproductive potential to use effective contraception during treatment with XALKORI and for at least 45 days after the final dose.

Males
Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use effective contraception during treatment with XALKORI and for at least 90 days after the final dose [see Nonclinical Toxicology (13.1)].

Infertility
Based on reproductive organ findings in animals, XALKORI may cause reduced fertility in males and females of reproductive potential. It is not known whether these effects on fertility are reversible [see Nonclinical Toxicology (13.1)].

8.9.2 Pediatric Use
The safety and efficacy of XALKORI in pediatric patients have not been established.

8.10 OVERDOSAGE
There have been no known cases of XALKORI overdose. There is no antidote for XALKORI.

11 DESCRIPTION
XALKORI (crizotinib) is an oral receptor tyrosine kinase inhibitor. The molecular formula for crizotinib is C21H22Cl2FN5O. The molecular weight is 450.34 daltons. Crizotinib is described chemically as 2,3-di-[(1-(2,6-Dichloro-3-fluorophenyl)ethoxy)-5-[(1-piperidin-4-yl)-1H-pyrazol-4-yl]pyridin-2-amine. The chemical structure of crizotinib is shown below:

Crizotinib is a white to pale-yellow powder with a pKa of 4.92 (piperidin-4-yl cation) and 5.6 (piperidin-4-yl cation). The solubility of crizotinib in aqueous media decreases over the range pH 1.6 to pH 8.2 from greater than 10 mg/mL to less than 0.1 mg/mL. The log of the distribution coefficient (octanol/water) at pH 7.4 is 1.65.

XALKORI capsules are supplied as print-hard shell capsules containing 250 mg or 200 mg of crizotinib together with colloidal silicon dioxide, microcrystalline cellulose, anhydrous dibasic calcium phosphate, sodium starch glycolate, magnesium stearate, and hard gelatin capsule shells as inactive ingredients. The pink opaque capsule shell components contain gelatin, titanium dioxide, and red iron oxide. The white opaque capsule shell components contain gelatin and titanium dioxide. The printing ink contains shellac, propylene glycol, sodium ammonia solution, potassium hydroxide, and black iron oxide.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Crizotinib is an inhibitor of receptor tyrosine kinases including ALK, Heterogeneous Growth Factor Receptor (HGFR, c-Met), ROS1 (c-ros), and Recepteur d’Origine Nantais (RON). Translocations which can affect the ALK gene resulting in the expression of oncogenic fusion proteins. The formation of ALK fusion proteins results in activation and dysregulation of the gene’s expression and signaling which can contribute to increased cell proliferation and survival in tumors expressing these proteins. Crizotinib demonstrated concentration-dependent inhibition of ALK, ROS1, and c-Met phosphorylation in cell-based assays using tumor cell lines and demonstrated antitumor activity in mice bearing tumor xenographs that expressed echinoderm microtubule-associated protein-like 4 (EML4)- or nucleophosmin (NPM)-ALK fusion proteins or c-Met.

12.2 Pharmacodynamics
Cardiac electrophysiology
In an ECG substudy conducted in 52 patients with ALK-positive NSCLC who received crizotinib 250 mg twice daily, the maximum mean QTcF (corrected QT by the Fridericia method) change from baseline was 12.3 ms (2-sided 95% upper CI: 19.5 ms). An exposure-QT analysis suggested a crizotinib plasma concentration-dependent increase in QTcF [see Warnings and Precautions (5.3)].

12.3 Pharmacokinetics
Absorption
Following a single oral dose, crizotinib was absorbed with median time to achieve peak concentration (Tmax) of 42 hours in patients.

Following single doses of crizotinib, the mean apparent plasma terminal half-life of crizotinib was 24 hours. The mean absolute bioavailability of crizotinib was 43% (range: 32% to 66%) following a single 250 mg oral dose.

A high-fat meal reduced crizotinib AUC from time zero to infinity (AUCinf) and maximum observed plasma concentration (Cmax) by approximately 14%. XALKORI can be administered with or without food.

Binding of crizotinib to human plasma proteins in vitro
Increased exposure to crizotinib occurred in patients with severe renal impairment (CLcr <30 mL/min) not requiring dialysis. Administer XALKORI at a dose of 250 mg taken orally once daily in patients with severe renal impairment not requiring dialysis [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)].

Distribution
The geometric mean volume of distribution (Vdss) of crizotinib was 1772 L following intravenous administration of a 50 mg dose, indicating extensive distribution into tissues from the plasma.

Binding of crizotinib to human plasma proteins in vitro is 91% and is independent of drug concentration. In vitro studies suggested that crizotinib is a substrate for P-glycoprotein (Pgp). The blood-to-plasma concentration ratio is approximately 1.

Elimination
Following single doses of crizotinib, the mean apparent plasma terminal half-life of crizotinib was 42 hours in patients.

12.5 Geriatric Use
Of the total number of patients with ALK-positive metastatic NSCLC in clinical studies of XALKORI (n=1669), 16% were 65 years or older and 3.8% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Clinical studies of XALKORI in patients with ROS1-positive metastatic NSCLC did not include sufficient numbers of patients age 65 years and older to determine whether they respond differently from younger patients. 

12.6 Hepatic Impairment
XALKORI has not been studied in patients with hepatic impairment. As crizotinib is extensively metabolized in the liver, hepatic impairment is likely to increase plasma crizotinib concentrations. Clinical studies excluded patients with AST or ALT greater than 2.5 times ULN, or greater than 5 times ULN, if due to liver metastases. Patients with total bilirubin greater than 1.5 times ULN were also excluded. Therefore, use caution in patients with hepatic impairment [see Clinical Pharmacology (12.3)].

12.7 Renal Impairment
No starting dose adjustment is needed for patients with mild (CLcr 60-89 mL/min) or moderate (CLcr 30-59 mL/min) renal impairment based on a population pharmacokinetic analysis. Increase the starting dose of crizotinib to 250 mg for patients with severe renal impairment (CLcr <30 mL/min) not requiring dialysis. Administer XALKORI at a dose of 250 mg taken orally once daily in patients with severe renal impairment not requiring dialysis [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)].
Following the administration of a single 250 mg radioabeled crizotinib dose to healthy subjects, 63% and 22% of the administered dose was recovered in feces and urine, respectively. Unchanged crizotinib represented approximately 53% and 23% of the administered dose in feces and urine, respectively.

The mean apparent clearance (CL/F) of crizotinib was lower at steady state (60 L/h) after 250 mg twice daily than after a single 250 mg oral dose (100 L/h), which was likely due to autoinduction of CYP3A by crizotinib after multiple dosing.

Metabolism
Crizotinib is predominantly metabolized by CYP3A4/5. The primary metabolic pathways in humans were oxidation of the piperidine ring to crizotinib lactam and O-dealkylation, with subsequent Phase 2 conjugation of O-dealkylated metabolites.

Specific populations
Hepatic impairment: As crizotinib is extensively metabolized in the liver, hepatic impairment is likely to increase plasma crizotinib concentrations. However, XALKORI has not been studied in patients with hepatic impairment. Clinical studies excluded patients with ALT or AST greater than 2.5 times ULN or greater than 5 times ULN if due to liver metastases. Patients with total bilirubin greater than 1.5 times ULN were excluded for safety reasons (see Use in Specific Populations (8.6)). The population pharmacokinetic analysis using the data from approximately 1200 patients with cancer who received XALKORI suggested that baseline total bilirubin (0.1 to 2.1 mg/dL) or AST levels (7 to 124 U/L) did not have a clinically relevant effect on the exposure of crizotinib.

Renal impairment: The pharmacokinetics of crizotinib were evaluated using the population pharmacokinetic analysis in patients with mild (CLcr 60-89 mL/min, n=433) and moderate (CLcr 30-59 mL/min, n=137) renal impairment. Mild or moderate renal impairment has no clinically relevant effect on the exposure of crizotinib.

A study was conducted in 7 patients with severe renal impairment (CLcr <30 mL/min) who did not require dialysis and 8 patients with normal renal function (CLcr ≥80 mL/min). All patients received a single 250 mg oral dose of XALKORI. The mean AUCinf for crizotinib increased by 79% in patients with severe renal impairment compared to those with normal renal function. Similar changes in AUC0-tau and Cmax were observed for the active metabolite of crizotinib (see Dosage and Administration (2.2) and Use in Specific Populations (8.7)).

Ethnicity: No clinically relevant difference in the exposure of crizotinib between Asian patients (n=171) and non-Asian patients (n=523) and non-Asian patients (n=691).

Age: Age has no effect on the exposure of crizotinib based on the population pharmacokinetic analysis.

Body weight and gender: No clinically relevant effect of body weight or gender on the exposure of crizotinib based on the population pharmacokinetic analysis.

Drug interactions
Effect of Other Drugs on Crizotinib
Strong CYP3A inhibitors: Co-administration of a single 150 mg oral dose of crizotinib with ketoconazole (200 mg twice daily), a strong CYP3A inhibitor, increased crizotinib AUCinf and Cmax by 24% and 12%, respectively, compared to crizotinib alone. However, the magnitude of effect of CYP3A inhibitors on steady-state crizotinib exposure has not been evaluated (see Drug Interactions (7.1)).

Strong CYP3A inducers: Co-administration of crizotinib (250 mg twice daily) with rifampin (600 mg once daily), a strong CYP3A inducer, decreased crizotinib steady-state AUC0-tau and Cmax by 64% and 79%, respectively, compared to crizotinib alone (see Drug Interactions (7.1)).

Gastric pH elevating medications: In healthy subjects, coadministration of a single 250 mg oral dose of crizotinib following administration of esomeprazole 40 mg daily for 5 days did not result in a clinically relevant change in crizotinib exposure (AUCinf decreased by 10% and no change in Cmax).

Effect of Crizotinib on Other Drugs
CYP3A substrates: Co-administration of crizotinib (250 mg twice daily for 28 days) in patients increased the AUC0-tau of oral midazolam 3.7-fold compared to midazolam alone, suggesting that crizotinib is a moderate inhibitor of CYP3A (see Drug Interactions (7.3)).

Other CYP substrates: In vitro studies suggest that clinical drug-drug interactions as a result of crizotinib-mediated inhibition of the metabolism of substrates for CYP1A2, CYP2C9, CYP2C19, or OATP2B6 are unlikely to occur.

Crizotinib is an inhibitor of CYP2B6 in vitro. Therefore, crizotinib may increase plasma concentrations of coadministered drugs that are predominantly metabolized by CYP2B6.

An in vitro study suggests that clinical drug-drug interactions as a result of crizotinib-mediated induction of the metabolism of substrates for CYP1A2, CYP2C9, CYP2C19, CYP2D6, and OATP2B6 are unlikely to occur.

Crizotinib inhibited the hepatic uptake transporter, organic cation transporter (OCT) 1, and renal uptake transporter, OCT2, in vitro at clinically relevant concentrations. Therefore, crizotinib has the potential to increase plasma concentrations of coadministered drugs that are substrates of OCT1 or OCT2.

Crizotinib did not inhibit the human hepatic uptake transport proteins, organic anion transporting polypeptides (OATP) B1 or OATP1B3, or the renal uptake transport proteins organic anion transporter (OAT) 1 or OAT3 in vitro at clinically relevant concentrations.

Other transporters: Crizotinib did not inhibit the hepatic efflux bile salt export pump transporter (BSEP) in vitro at clinically relevant concentrations.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenicity studies with crizotinib have not been performed.

Crizotinib was genotoxic in an in vitro micronucleus assay in Chinese Hamster Ovary cultures, in an in vitro human lymphocyte chromosome aberration assay, and in vivo rat bone marrow micronucleus assays. Crizotinib was not mutagenic in vitro (Ames) assay. No specific studies with crizotinib have been conducted in animals to evaluate the effect on fertility; No specific studies with crizotinib have been conducted in animals to evaluate the effect on fertility; No specific studies with crizotinib have been conducted in animals to evaluate the effect on fertility.
Previously Treated ALK-Positive Metastatic NSCLC - Study 2

The efficacy and safety of XALKORI as monotherapy for the treatment of 347 patients with ALK-positive metastatic NSCLC, previously treated with 1 platinum-based chemotherapy regimen, were demonstrated in a randomized, multicenter, open-label, active-controlled study (Study 2). The major efficacy outcome was PFS according to investigator assessment. Additional efficacy outcomes included ORR as assessed by IRR, DOR, and OS.

Patients were randomized to receive XALKORI 250 mg orally twice daily (n=173) or chemotherapy (n=174). Chemotherapy consisted of pemetrexed 500 mg/m² (if pemetrexed-naïve; n=99) or docetaxel 75 mg/m² (n=72) intravenously (IV) every 21 days. Patients in both treatment arms continued treatment until documented disease progression, intolerance to therapy, or the investigator determined that the patient was no longer experiencing clinical benefit. Randomization was stratified by ECOG performance status (0-1, 2), brain metastases (present, absent), and prior EGFR tyrosine kinase inhibitor treatment (yes, no). Patients were required to have ALK-positive NSCLC as identified by the FDA-approved assay, Vysis ALK Break-Apart FISH Probe Kit, prior to randomization. A total of 112 (64%) patients randomized to the chemotherapy arm subsequently received XALKORI after disease progression.

The demographic characteristics of the overall study population were 56% female, median age of 50 years, baseline ECOG performance status 0 or 1 (90%), 52% White and 45% Asian, 4% current smokers, 33% past smokers, and 63% never smokers. The disease characteristics of the overall study population were metastatic disease in at least 95% of patients and at least 93% of patients’ tumors were classified as adenocarcinoma histology.

Study 2 demonstrated a statistically significant improvement in PFS in the patients treated with XALKORI. Table 8 and Figure 2 summarize the efficacy results.

Table 8. Previously Treated ALK-Positive Metastatic NSCLC - Efficacy Results

<table>
<thead>
<tr>
<th></th>
<th>XALKORI (N=173)</th>
<th>Chemotherapy (N=174)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Events (%)</td>
<td>100 (58%)</td>
<td>127 (73%)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>84 (49%)</td>
<td>119 (68%)</td>
</tr>
<tr>
<td>Death</td>
<td>16 (9%)</td>
<td>8 (5%)</td>
</tr>
<tr>
<td>Median, Months (95% CI)</td>
<td>7.7 (6.0, 8.8)</td>
<td>3.0* (2.6, 4.3)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.49 (0.37, 0.64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Overall Survivala</td>
<td>49 (28%)</td>
<td>47 (27%)</td>
</tr>
<tr>
<td>Median, Months (95% CI)</td>
<td>20.3 (18.1, NR)</td>
<td>22.8 (18.6, NR)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.02 (0.68, 1.54)</td>
<td>0.92</td>
</tr>
<tr>
<td>Tumor Responses (Based on IRR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Objective Response Rate % (95% CI)</td>
<td>65% (58.72)</td>
<td>20% (14, 26)</td>
</tr>
<tr>
<td>CR, n (%)</td>
<td>1 (0.6%)</td>
<td>0</td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>112 (65%)</td>
<td>34 (20%)</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Duration of Response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, Months (95% CI)</td>
<td>7.4 (6.1, 9.7)</td>
<td>5.6 (3.4, 8.3)</td>
</tr>
</tbody>
</table>

HR=hazard ratio; CI=confidence interval; IRR=investigator assessment; NR=not reached; CR=complete response; PR=partial response.

Figure 2. Kaplan-Meier Curves of Progression-Free Survival as Assessed by IRR in Study 2

14.2 ROS1-Positive Metastatic NSCLC

The efficacy and safety of XALKORI was investigated in a multicenter, single-arm study (Study 3), in which patients with ROS1-positive metastatic NSCLC received XALKORI 250 mg orally twice daily. Patients were required to have histologically-confirmed advanced NSCLC with a ROS1 rearrangement, age 18 years or older, ECOG performance status of 0, 1, or 2, adequate organ function, and measurable disease. The efficacy outcome measures were ORR and DOR according to RECIST version 1.0 as assessed by IRR and investigator, with imaging performed every 8 weeks for the first 60 weeks.

Baseline demographic and disease characteristics were female (56%), median age of 53 years, baseline ECOG performance status of 0 or 1 (98%), White (54%), Asian (42%), past smokers (22%), never smokers (78%), metastatic disease (92%), adenocarcinoma (96%), no prior systemic therapy for metastatic disease (14%), and prior platinum-based chemotherapy for metastatic disease (80%). The ROS1 status of NSCLC tissue samples was determined by laboratory-developed break-apart FISH (96%) or RT-PCR (4%) clinical trial assays. For assessment by FISH, ROS1 positivity required that >15% of a minimum of 50 evaluated nuclei contained a ROS1 gene rearrangement. Efficacy results are summarized in Table 9.

<table>
<thead>
<tr>
<th>Efficacy Parameters</th>
<th>IRR (N=50)</th>
<th>Investigator-Assessed (N=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective Response Rate (95% CI)</td>
<td>66% (51, 79)</td>
<td>72% (58, 84)</td>
</tr>
<tr>
<td>Complete Response, n</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Partial Response, n</td>
<td>32</td>
<td>31</td>
</tr>
<tr>
<td>Duration of Responsea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, Months (95% CI)</td>
<td>18.5 (12.7, NR)</td>
<td>NR (14.5, NR)</td>
</tr>
</tbody>
</table>

IRR=investigator assessment; CI=confidence interval; NR=not reached.

* As assessed by RECIST version 1.0

16 HOW SUPPLIED/STORAGE AND HANDLING

- 250 mg capsules
  - Hard gelatin capsule with pink opaque cap and body, printed with black ink “Pfizer” on the cap, “CRZ 250” on the body; available in: Bottles of 60 capsules: NDC 0069-8140-20

- 200 mg capsules
  - Hard gelatin capsule with pink opaque cap and white opaque body, printed with black ink “Pfizer” on the cap, “CRZ 200” on the body; available in: Bottles of 60 capsules: NDC 0069-8141-20

Store at room temperature 20 to 25°C (68 to 77°F); excursions permitted between 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hepatotoxicity

Advise patients to immediately report symptoms of hepatotoxicity [see Warnings and Precautions (5.1)].

Interstitial Lung Disease (Pneumonitis)

Advise patients to immediately report any new or worsening pulmonary symptoms [see Warnings and Precautions (5.2)].

Bradycardia

Advise patients to report any symptoms of bradycardia and to inform their healthcare provider about the use of any heart or blood pressure medications [see Warnings and Precautions (5.4)].

Severe Visual Loss

Inform patients of the potential risk of severe visual loss and to immediately contact their healthcare provider if they develop severe visual loss. Inform patients that visual changes such as perceived flashes of light, blurry vision, light sensitivity, and floaters are commonly reported adverse events and may occur while driving or operating machinery. The onset of visual disorders most commonly occurs during the first week of treatment [see Warnings and Precautions (5.5) and Adverse Reactions (6)].

Drug Interactions

Inform patients to avoid grapefruit or grapefruit juice while taking XALKORI. Advise patients to inform their healthcare providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products [see Drug Interactions (7)].

Dosing and Administration

Advise patients to take XALKORI with or without food and swallow XALKORI capsules whole.

If a patient misses a dose, advise the patient to take it as soon as remembered unless it is less than 6 hours until the next dose, in which case, advise the patient not to take the missed dose. If a patient vomits after taking a dose of XALKORI, advise the patient not to take an extra dose, but to take the next dose at the regular time.

Embro-Fetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.6) and Use in Specific Populations (8.1)].

Advise females of reproductive potential to use effective contraception during treatment with XALKORI and for at least 45 days after the final dose [see Use in Specific Populations (8.3)].

Females and Males of Reproductive Potential

Advise females and males of reproductive potential of the potential for reduced fertility from XALKORI [see Use in Specific Populations (8.3) and Nonclinical Toxicology (13.1)].

Advise male patients with female partners of reproductive potential to use condoms during treatment with XALKORI and for at least 45 days after the final dose [see Use in Specific Populations (8.3)].

Lactation

Advise females not to breastfeed during treatment with XALKORI and for 45 days after the final dose [see Use in Specific Populations (8.2)].

Infertility

Advise females and males of reproductive potential of the potential for reduced fertility from XALKORI [see Use in Specific Populations (8.3)].

This product’s labeling may have been updated. For full prescribing information, please visit www.XALKORI.com.
What is the most important information I should know about XALKORI?

XALKORI may cause serious side effects, including:

- **Liver problems.** XALKORI may cause life-threatening liver injury that may lead to death. Your healthcare provider should do blood tests at least every month to check your liver during treatment with XALKORI. Tell your healthcare provider right away if you get any of the following new or worsening symptoms:
  - yellowing of your skin or the white part of your eyes
  - severe tiredness
  - dark or brown (tea color) urine
  - nausea or vomiting
  - decreased appetite
  - pain on the right side of your stomach
  - bleed or bruise more easily than normal
  - itching

- **Lung problems (pneumonitis).** XALKORI may cause life-threatening lung problems that may lead to death. Symptoms may be similar to those symptoms from lung cancer. Tell your healthcare provider right away if you have any new or worsening symptoms, including:
  - trouble breathing or shortness of breath
  - cough with or without mucus
  - fever

- **Heart problems.** XALKORI may cause very slow, very fast, or abnormal heartbeats. Your healthcare provider may check your heart during treatment with XALKORI. Tell your healthcare provider right away if you feel dizzy or faint or have abnormal heartbeats. Tell your healthcare provider if you take any heart or blood pressure medicines.

- **Vision problems.** Vision problems are common with XALKORI. These problems usually happen within 1 week of starting treatment with XALKORI. Vision problems with XALKORI can be severe and may cause partial or complete loss of vision in one or both eyes. Your healthcare provider may stop XALKORI and refer you to an eye healthcare provider if you develop severe vision problems during treatment with XALKORI. Tell your healthcare provider right away if you have any loss of vision or any change in vision, including:
  - double vision
  - seeing flashes of light
  - blurry vision
  - light hurting your eyes
  - new or increased floaters

- See “What are possible side effects of XALKORI?” for more information about side effects.

What is XALKORI?

XALKORI is a prescription medicine that is used to treat people with non-small cell lung cancer (NSCLC) that has spread to other parts of the body and is caused by a defect in either a gene called ALK (anaplastic lymphoma kinase) or a gene called ROS1.

It is not known if XALKORI is safe and effective in children.

What should I tell my healthcare provider before taking XALKORI?

**Before you take XALKORI, tell your healthcare provider if you:**

- have heart problems, including a condition called long QT syndrome
- have liver or kidney problems
- have vision or eye problems
- have any other medical conditions
- are pregnant, or plan to become pregnant. XALKORI can harm your unborn baby.
  - **Females** who are able to become pregnant should use effective birth control during treatment with XALKORI and for at least 45 days after the final dose of XALKORI.
  - **Males** who have female partners who can become pregnant should use condoms during treatment with XALKORI and for at least 90 days after the final dose of XALKORI.
  - Talk to your healthcare provider about birth control methods that may be right for you.
  - If you or your partner becomes pregnant, tell your healthcare provider right away.
- are breastfeeding or plan to breastfeed. It is not known if XALKORI passes into your breast milk. Do not breastfeed during treatment with XALKORI and for 45 days after the final dose. Talk to your healthcare provider about the best way to feed your baby during this time.

**Tell your healthcare provider about the medicines you take, including** prescription medicines, over-the-counter medicines, vitamins, and herbal supplements.

How should I take XALKORI?

- Take XALKORI exactly as your healthcare provider tells you.
- Swallow XALKORI capsules whole.
- You may take XALKORI with or without food.
- Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with XALKORI if you have certain side effects. Do not change your dose or stop taking XALKORI unless your healthcare provider tells you.
- If you miss a dose, take it as soon as you remember. If it is close to your next dose (within 6 hours), just take your next dose at your regular time.
- If you vomit after taking a dose of XALKORI, do not take an extra dose, just take your next dose at your regular time.
What should I avoid while taking XALKORI?

- You should not drink grapefruit juice or eat grapefruit during your treatment with XALKORI. It may increase the amount of XALKORI in your blood to a harmful level.
- XALKORI can cause changes in your vision, dizziness, and tiredness. If you have these symptoms avoid driving a car, using machinery, or doing anything that needs you to be alert.

What are the possible side effects of XALKORI?

XALKORI may cause serious side effects, including:
- See “What is the most important information I should know about XALKORI?”

The most common side effects of XALKORI include:
- vision problems. See “What is the most important information I should know about XALKORI?”
- nausea
- diarrhea
- vomiting
- swelling of your hands, feet, face, and eyes
- constipation
- increased liver function blood test results. See “What is the most important information I should know about XALKORI?”
- tiredness
- decreased appetite
- upper respiratory infection
- dizziness
- feeling of numbness or tingling in the extremities

XALKORI may cause decreased fertility in females and males. In females, this could affect your ability to become pregnant. In males, this could affect your ability to father a child. Talk to your healthcare provider if you have concerns about fertility.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of XALKORI. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store XALKORI?

- Store XALKORI at room temperature between 68°F to 77°F (20°C to 25°C).

Keep XALKORI and all medicines out of the reach of children.

General information about XALKORI

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use XALKORI for a condition for which it was not prescribed. Do not give XALKORI to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for more information about XALKORI that is written for health professionals.

What are the ingredients in XALKORI?

Active ingredient: crizotinib

Inactive ingredients: colloidal silicon dioxide, microcrystalline cellulose, anhydrous dibasic calcium phosphate, sodium starch glycolate, and magnesium stearate.

Pink opaque capsule shell contains: gelatin, titanium dioxide, and red iron oxide.

White opaque capsule shell contains: gelatin and titanium dioxide.

Printing ink contains: shellac, propylene glycol, strong ammonia solution, potassium hydroxide, and black iron oxide.

Distributed by

Pfizer Labs
Division of Pfizer Inc. NY, NY 10017

LAB-0441-8.0

For more information, go to www.XALKORI.com.