XALKORI® (crizotinib) 250 mg capsules is an oral medicine 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, and for the treatment of patients with metastatic NSCLC whose tumors are ROS1-positive. XALKORI received its first approval in 2011 under the U.S. Food and Drug Administration (FDA) accelerated approval process. Today, XALKORI has become the first-line standard of care for ALK+ metastatic NSCLC and is the only FDA-approved treatment indicated for two distinct biomarkers, ALK and ROS1, in metastatic NSCLC.

**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.

Please see the full Prescribing Information at the end of this document.

*FDA grants accelerated approval of XALKORI (crizotinib) for the following indication: treatment of patients with locally advanced or metastatic NSCLC that is ALK-positive as detected by an FDA-approved test. This indication is based on response rate. There are no data available demonstrating improvement in patient-reported outcomes or survival with XALKORI.*
Intestinal 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, bradycardyrhythmias, 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.

Bradyarrhythmia: 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. 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 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. Arrange for the patient to avoid exposure to the drug if there is even a possibility of pregnancy. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraceptive 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 (n=171). In general, XALKORI was well tolerated. 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%), abdominal pain (26% vs 12%), and fatigue (29% vs 16%). The most frequent reactions occurring at a ≥2% higher incidence with XALKORI vs chemotherapy were dyspepsia (13% vs 2%), nausea (5% vs 3%), vomiting (11% vs 3%), and constipation (11% vs 4%). 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.

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

Please see full Prescribing Information at www.XALKORI.com and at the end of this document.

XALKORI Indications

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. XALKORI is indicated for the treatment of patients with metastatic NSCLC whose tumors are ROS1-positive.

References


To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.
a dose of XALKORI, take the next dose at the regular time.

missed, make up that dose unless the next dose is due within 6 hours. If vomiting occurs after taking

Reduce dose as below, if 1 or more dose reductions are necessary due to adverse reactions of

The recommended dose of XALKORI in patients with severe renal impairment [creatinine clearance

The recommended dose of XALKORI is 250 mg orally, twice daily until disease progression or no

Select patients for the treatment of metastatic NSCLC with XALKORI based on the presence of ALK

XALKORI is indicated for the treatment of patients with metastatic NSCLC whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test. (1.1)

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. (1.1)

ROS1-Positive Metastatic NSCLC

XALKORI is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are ROS1-positive. (1.2)

XALKORI is indicated for the treatment of patients with:

- metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase

- metastatic NSCLC whose tumors are ROS1-positive. (1.2)

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

Recommended Dosing

Renal Impairment: 250 mg orally, once daily in 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

7.3  Drugs Whose Plasma Concentrations May Be Altered By Crizotinib

DRUG INTERACTIONS

CYP3A Substrates: Avoid concurrent use of XALKORI with strong CYP3A inhibitors. (7.1)

CYP3A Inducers: Avoid concurrent use of XALKORI with strong CYP3A inducers. (7.2)

CYP3A Substrates: Avoid concurrent use of XALKORI with CYP3A substrates with narrow therapeutic indices. (7.3)

USE IN SPECIFIC POPULATIONS

Lactation: Do not breastfeed while taking XALKORI. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 4/2016

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 250 mg taken orally once 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>Alkaline phosphatase (ALP) or aspartate aminotransferase (AST) elevation greater than 5 times upper limit of normal (ULN) with total bilirubin less than or equal to 1.5 times ULN</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 the same dose schedule.</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>

Adverse Events (NCI CTCAE) version 4.0:

- 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 250 mg taken orally once daily
- Permanently discontinue if unable to tolerate XALKORI 250 mg taken orally once daily

Dose reduction guidelines are provided in Tables 1 and 2.

- Interstitial Lung Disease (ILD)/Pneumonitis: Occurred in 2.9% of patients. Permanently discontinue in patients with ILD/pneumonitis. (5.2)
- QT Interval Prolongation: Occurred in 2.1% of patients. Monitor electrocardiograms and electrolytes in patients who have a history of or predisposition for QTc prolongation, or who are taking medications that prolong QT. Temporarily suspend, dose reduce, or permanently discontinue XALKORI. (5.3)
- Bradycardia: XALKORI can cause bradycardia. Monitor heart rate and blood pressure regularly. Temporarily suspend, dose reduce, or permanently discontinue XALKORI. (5.4)
- Severe Visual Loss: Reported in 0.2% of patients. Discontinue XALKORI in patients with severe visual loss. Perform an ophthalmological evaluation. (5.5)
- Emesis/Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception. (5.6, 8.1, 8.3)

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

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

8.3 Females and Males of Reproductive Potential

8.4 Pediatric Use

8.5 Neonates

8.6 Hepatic Impairment

8.7 Renal Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

14.1 ALK-Positive Metastatic NSCLC

14.2 ROS1-Positive Metastatic NSCLC

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.
60 bpm or above, re-evaluate the use of concomitant medications, and adjust the dose of XALKORI.

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 or above, and if concomitant medications can be adjusted or discontinued, restart XALKORI at 250 mg once daily with frequent monitoring [see Dosage and Administration (2.3) and Adverse Reactions (6)].

5.5 Severe Visual Loss
Across all clinical trials, the incidence of Grade 4 visual field defect with vision loss was 0.2% (4/1719). Optic atrophy and optic nerve disorder have been reported as potential causes of vision loss.

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 consisting of best corrected visual acuity, retinal photographs, visual fields, optical coherence tomography (OCT) and other examinations as appropriate for new onset of severe visual loss. There is insufficient information to characterize the risks of resumption of XALKORI in patients with a severe visual loss; a decision to resume XALKORI should consider the potential benefits to the patient.

5.6 Embryo-Fetal Toxicity
Based on its mechanism of action, XALKORI can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, oral administration of crotizibotin in pregnant rats during organogenesis at exposures similar to those observed with the maximum recommended human dose resulted in embryotoxicity and fetotoxicity. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with XALKORI and for at least 45 days following the final dose [see Use in Specific Populations (8.1, 8.3)].

Anticipate NSCLC from a single-arm study (Study 3).

5.5 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), 2, 3, a single arm trial (n=1083) of ALK-positive NSCLC, and an additional ALK-positive NSCLC extension 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-arm study (Study 3).

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. XALKORI was received in a randomized, multicenter, open-label, active-controlled trial (Study 1). Patients in the XALKORI arm (n=171) received XALKORI 250 mg orally twice daily until documented disease progression, intolerance to therapy, or the investigator determined that the patient was no longer experiencing clinical benefit. Median progression-free survival time in the XALKORI arm was 6 months. Patients received pemetrexed 500 mg/m² in combination with cisplatin 75 mg/m² (n=91) or carboplatin at a dose calculated to produce an area under the concentration-time curve (AUC) of 5 or 6 mg min/mL (n=80). Chemotherapy was given by intravenous infusion every 3 weeks for up to 6 cycles, in the absence of dose-limiting chemotherapy-related toxicities. After 6 cycles, patients remained on study with no additional anticancer treatment, and tumor assessments continued until documented disease progression.

The median duration of study 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 46% 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% of 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 for treatment adverse reactions was 8.2%. The most frequent adverse reactions that led to permanent discontinuation in XALKORI-treated patients were elevated 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.
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 (1%)</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vision disorder</td>
<td>71 (42%)</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>46 (27%)</td>
<td>36 (22%)</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>Dyspnea</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 (11%)</td>
<td>10 (6%)</td>
</tr>
<tr>
<td>Dysesthesia</td>
<td>26 (15%)</td>
<td>5 (3%)</td>
</tr>
<tr>
<td>Headache</td>
<td>22 (13%)</td>
<td>15 (9%)</td>
</tr>
</tbody>
</table>
| Laboratory Abnormalities with Grade 3 or 4 Incidence of ≥4% in XALKORI-Treated Patients in Study 1

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>XALKORI Any Grade (%)</th>
<th>XALKORI Grade 3-4 (%)</th>
<th>Chemotherapy Any Grade (%)</th>
<th>Chemotherapy Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>52 (31%)</td>
<td>11 (6%)</td>
<td>59 (35%)</td>
<td>16 (10%)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>48 (28%)</td>
<td>7 (4%)</td>
<td>53 (31%)</td>
<td>13 (8%)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT elevation</td>
<td>79 (46%)</td>
<td>15 (9%)</td>
<td>33 (20%)</td>
<td>7 (4%)</td>
</tr>
<tr>
<td>AST elevation</td>
<td>66 (39%)</td>
<td>8 (5%)</td>
<td>28 (17%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>32 (19%)</td>
<td>10 (6%)</td>
<td>21 (13%)</td>
<td>6 (4%)</td>
</tr>
</tbody>
</table>

Previously Treated ALK-Positive Metastatic NSCLC - Study 2

The data in Table 5 are derived from 343 patients with ALK-positive metastatic NSCLC enrolled in a randomized, multicenter, active-controlled, open-label trial (Study 2). Patients in the XALKORI arm (n=172) received XALKORI 250 mg orally twice daily until documented disease progression, intolerance to therapy, or the investigator determined that the patient was no longer experiencing clinical benefit. A total of 171 patients in the chemotherapy arm received pemetrexed 500 mg/m² (n=99) or docetaxel 75 mg/m² (n=72) by intravenous infusion every 3 weeks until documented disease progression, intolerance to therapy, or the investigator determined that the patient was no longer experiencing clinical benefit. A total of 169 patients in the chemotherapy arm received pemetrexed 500 mg/m² and cisplatin 100 mg/m² or pemetrexed 500 mg/m² and carboplatin 375 mg/m² by intravenous infusion every 3 weeks until documented disease progression, intolerance to therapy, or the investigator determined that the patient was no longer experiencing clinical benefit.

The median duration of study treatment was 7.1 months for patients who received XALKORI and 2.8 months for patients who received chemotherapy. Across the 347 patients who were randomized to study treatment (345 received at least 1 dose of study treatment), the median age was 59 years; 14% of patients were older than 65 years. A total of 46% of patients were female and 45% of patients were Asian.

Serious adverse reactions were reported in 64 patients (37.2%) treated with XALKORI and 40 patients (23.4%) in the chemotherapy arm. The most frequent serious adverse reactions reported in patients treated with XALKORI were pneumonia (4.1%), pulmonary embolism (3.3%), dyspnea (2.3%), and ILD (2.9%). Fatal adverse reactions in XALKORI-treated patients in Study 2 occurred in 9 (5%) patients, consisting of: acute respiratory distress syndrome, arrhythmia, dyspnea, pneumonia, pneumonitis, pulmonary embolism, ILD, respiratory failure, and sepsis.

Dose reductions due to adverse reactions were required in 16% of XALKORI-treated patients. The most frequent adverse reactions that led to dose reduction in the patients treated with XALKORI were ALT elevation (7.6%) including some patients with concurrent AST elevation, QTc prolongation (2.9%), and neuropenia (2.3%). 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 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>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>XALKORI (N=172)</th>
<th>Chemotherapy (Pemetrexed or Docetaxel) (N=171)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrocardiogram QT prolonged Bradycardia</td>
<td>5 (3%)</td>
<td>0 (%)</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vision disorder</td>
<td>60 (35%)</td>
<td>9 (5%)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>22 (13%)</td>
<td>8 (5%)</td>
</tr>
<tr>
<td>Dysesthesia</td>
<td>26 (15%)</td>
<td>9 (5%)</td>
</tr>
<tr>
<td>Syncope</td>
<td>3 (2%)</td>
<td>0 (%)</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vision disorder</td>
<td>60 (35%)</td>
<td>9 (5%)</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>22 (13%)</td>
<td>8 (5%)</td>
</tr>
<tr>
<td>Dysesthesia</td>
<td>26 (15%)</td>
<td>9 (5%)</td>
</tr>
<tr>
<td>Syncope</td>
<td>3 (2%)</td>
<td>0 (%)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>XALKORI Any Grade (%)</th>
<th>XALKORI Grade 3-4 (%)</th>
<th>Chemotherapy Any Grade (%)</th>
<th>Chemotherapy Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>49 (29%)</td>
<td>12 (7%)</td>
<td>28 (17%)</td>
<td>12 (7%)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>51 (30%)</td>
<td>9 (5%)</td>
<td>60 (36%)</td>
<td>25 (15%)</td>
</tr>
</tbody>
</table>

Adverse reactions were graded using NCI CTCAE version 4.0. Includes cases reported within the clustered terms.

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>XALKORI Any Grade (%)</th>
<th>XALKORI Grade 3-4 (%)</th>
<th>Chemotherapy Any Grade (%)</th>
<th>Chemotherapy Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>49 (29%)</td>
<td>12 (7%)</td>
<td>28 (17%)</td>
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</tr>
<tr>
<td>Lymphopenia</td>
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<td>60 (36%)</td>
<td>25 (15%)</td>
</tr>
</tbody>
</table>

Adverse reactions were graded using NCI CTCAE version 4.0. Includes cases reported within the clustered terms.

ROS1-Positive Metastatic NSCLC - Study 3

The safety profile of XALKORI from Study 3, which was evaluated in 50 patients with ROS1-positive metastatic NSCLC, was generally consistent with the safety profile of XALKORI evaluated in patients with ALK-positive metastatic NSCLC (n=1669). Vision disorders occurred in 92% of patients in Study 3; 90% were Grade 1 and 2% were Grade 2. The median duration of exposure to XALKORI was 34.4 months.

Description of Selected Adverse Drug Reactions

Vision disorders

Vision disorders, most commonly visual impairment, photopsia, blurred vision, or vitreous floaters, occurred in 1084 (63.1%) of 1719 patients. The majority (95%) of these patients had Grade 1 visual impairment. There were 13 (0.8%) patients with Grade 3 and 4 (0.2%) patients with Grade 4 visual impairment.

Based on the Visual Symptom Assessment Questionnaire (VSAS-42A), patients treated with XALKORI in Studies 1 and 2 reported a higher incidence of visual disturbances compared to patients treated with chemotherapy. The onset of vision disorder generally was within the first week of drug administration. The majority of patients on the XALKORI arms in Studies 1 and 2 (≥5%) reported visual disorders.

A total of 1084 (63.1%) of 1719 patients. The majority (95%) of these patients had Grade 1 visual impairment. There were 13 (0.8%) patients with Grade 3 and 4 (0.2%) patients with Grade 4 visual impairment.

Selected adverse drug reactions included vision disorders, most commonly visual impairment, photopsia, blurred vision, or vitreous floaters, which occurred in a frequency of 4-7 days each week, lasting up to 1 month, and
had mild or no impact (scores 0 to 3 out of a maximum score of 10) on daily activities as captured in the VSAQ-ALK questionnaire.

Neuropathy
Neuropathy, most commonly sensory in nature, occurred in 435 (25%) of 1719 patients. Most events (95%) were Grade 1 or Grade 2 in severity.

Renal cysts
Renal cysts were experienced by 52 (3%) of 1719 patients.

The majority of renal cysts in XALKORI-treated patients were complex. Local cystic invasion beyond the kidney occurred, in some cases with imaging characteristics suggestive of abscess formation. However, across clinical trials no renal abscesses were confirmed by microbiology tests.

Renal impairment
The estimated glomerular filtration rate (eGFR) decreased from a baseline median of 96.42 mL/min/1.73 m² (n=1681) to a median of 80.23 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 median 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.

7 DRUG INTERACTIONS

7.1 Drugs That May Increase Crizotinib Plasma Concentrations
Coadministration of crizotinib with strong cytochrome P450 (CYP) 3A inhibitors increases crizotinib plasma concentrations [see Clinical Pharmacology (12.3)]. Avoid concomitant use of strong CYP3A inhibitors, including but not limited to atazanavir, clarithromycin, indinavir, irtraconazole, ketoconazole, nefazodone, neflinavar, ritonavir, saquinavir, telithromycin, trofarlozine, and voriconazole. Avoid grapefruit or grapefruit juice which may also increase plasma concentrations of crizotinib. Exercise caution with concomitant use of moderate CYP3A inhibitors.

7.2 Drugs That May Decrease Crizotinib Plasma Concentrations
Coadministration of crizotinib with strong CYP3A inducers decreases crizotinib plasma concentrations [see Clinical Pharmacology (12.3)]. Avoid concomitant use of strong CYP3A inducers, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's Wort.

7.3 Drugs Whose Plasma Concentrations May Be Altered By Crizotinib
Crizotinib is a potential inhibitor of CYP3A. Coadministration of crizotinib with drugs known to inhibit CYP3A substrates with narrow therapeutic range, including but not limited to astemizole, cisapride, itraconazole, ketoconazole, macrolide antibiotics, midazolam, quinidine, ranitidine, and voriconazole, is not recommended.

8 USE IN SPECIFIC POPULATIONS

8.1 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 population in the U.S. general population is 2 to 4% and 15 to 20%, respectively. In pregnant women treated with XALKORI, dose reductions of the CYP3A substrates may be required due to adverse reactions.

Data Animal Data
Crizotinib was administered to pregnant rats and rabbits during organogenesis to study the effects on embryo-fetal development. Postimplantation loss was increased at doses ≥50 mg/kg/day (approximately 0.6 times the recommended human dose based on AUC) in rats. No teratogenic effects were observed in rats at doses up to the maternally toxic dose of 200 mg/kg/day (approximately 2.7 times the recommended human dose based on AUC) or in rabbits at doses of up to 60 mg/kg/day (approximately 1.6 times the recommended human dose based on AUC), though fetal body weights were reduced at these doses.

8.2 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.

8.3 Females and Males of Reproductive Potential
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 condoms 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 females and males of reproductive potential. It is not known whether these effects on fertility are reversible [see Nonclinical Toxicology (13.1)].

8.4 Pediatric Use
The safety and efficacy of XALKORI in pediatric patients has not been established.

Animal Data
Decreased bone formation in growing long bones was observed in immature rats at 150 mg/kg/day following once daily dosing for 28 days (approximately 5.4 times the recommended human dose based on AUC). Other toxicities of potential concern to pediatric patients have not been evaluated in juvenile animals.

8.5 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 younger and older 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.

8.6 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)].

8.7 Renal Impairment
No starting dose adjustment is needed for patients with mild (CLCr >50 mL/min) or moderate (CLCr 30-50 mL/min) renal impairment based on a population pharmacokinetic analysis. Increase the crizotinib dose 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)].

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 C20H17ClF2N5O3S. The molecular weight is 450.34 daltons. Crizotinib is described chemically as (R)-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:

![Chemical Structure of Crizotinib](image-url)

Crizotinib is a white to pale-yellow powder with a pKa of 4.0 (piperidinyl cation) and 5.6 (pyridinium 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-hardshell 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 shell, propylene glycol, strong 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, Hepatocyte Growth Factor Receptor (HGFR, c-Met), ROS1 (c-ros), and Receptor of Origin Nantais (RON). Translocations 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 phosphorylations in cell-based assays using tumor cell lines and demonstrated antitumor activity in mice bearing tumor xenografts 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 QTc (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 QTc [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 2.5 hours following a 250 mg oral dose. A high-fat meal reduced crizotinib AUC from time zero to infinity (AUCinf) and maximum observed concentration (Cmax) by approximately 14%, XALKORI can be administered with or without food [see Dosage and Administration (2.2)].

Distribution
The geometric mean volume of distribution (Vd) of crizotinib was 1727 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 (P-gp). 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.
Body weight and gender: (n=523) and non-Asian patients (n=691). Strong CYP3A inhibitors: Drug interactions crizotinib based on the population pharmacokinetic analysis.

Ethnicity: No clinically relevant difference in the exposure of crizotinib between Asian patients (n=147) and non-Asian patients (n=335).

Age: 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 AUCv and Cmax by approximately 2-fold and 1.4-fold, 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 AUCv and Cmax by 64% and 79%, respectively, compared to crizotinib administration alone (see Drug Interactions (7.2)).

Gastric pH elevating medications: In healthy subjects, co-administration 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 AUCv and oral Cmax of 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, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 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, CYP2C8, CYP2C9, CYP2C19, or UGT3A4 are unlikely to occur.

**UGT substrates:** In vitro studies suggest that clinical drug-drug interactions as a result of crizotinib-mediated inhibition of the metabolism of drugs that are substrates for uridine diphosphate glucuronosyltransferase (UGT1A1, UGT1A4, UGT1A6, UGT1A9, or UGT2B7 are unlikely to occur. However, the magnitude of effect of crizotinib on the metabolism of substrates for CYP1A2, CYP2C8, CYP2C9, CYP2C19, or UGT3A4 are unlikely to occur.

Crizotinib inhibited the hepatic uptake transporter, organic cation transporter (OCT1), 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 inhibited the organic anion transporting polypeptides (OATP) B1 (OATP B1) or OATP B1, or the renal uptake transport proteins organic anion transporter (DAT) 1 or OAT3 in vitro at clinically relevant concentrations.

Other transporters: Crizotinib did not inhibit the efflux bili 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 reported. 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 in the bacterial reverse mutation (Ames) assay.

No specific studies with crizotinib have been conducted in animals to evaluate the effect on fertility; however, crizotinib is considered to have the potential to impair reproductive function and fertility in humans based on the non-clinical toxicity studies in the rat. Findings observed in the male reproductive tract included testicular pachytane spermatocyte degeneration in rats given greater than or equal to 50 mg/kg/day for 28 days (greater than 1.7 times the recommended human dose based on AUC). Findings observed in the female reproductive tract included single-cell necrosis of ovarian follicles of a rat given 500 mg/kg/day (approximately 10 times the recommended human dose based on body surface area) for 3 days.

### 14 CLINICAL STUDIES

#### 14.1 ALK-Positive Metastatic NSCLC

**Previously Untreated ALK-Positive Metastatic NSCLC - Study 1**

The efficacy and safety of XALKORI for the treatment of patients with ALK-positive metastatic NSCLC, who had not received previous systemic treatment for advanced disease, was demonstrated in a randomized, multicenter, open-label, active-controlled study (Study 1). Patients were required to have an ALK-positive NSCLC as identified by the FDA-approved assay, Vysis ALK-Break Apart fluorescence in situ hybridization (FISH) Probe Kit, prior to randomization. The major efficacy outcome measure was progression-free survival (PFS) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 as assessed by independent radiology review (IRR) committee. Additional efficacy outcome measures included objective response rate (ORR) as assessed by IRR, duration of response (DOR), and overall survival (OS). Patient-reported lung cancer symptoms were assessed at baseline and periodically during treatment.

Patients were randomized to receive XALKORI (n=172) or chemotherapy (n=171). Randomization was stratified by Eastern Cooperative Operative Group (ECOG) performance status (0-1, 2), race (Asian, non-Asian), and brain metastases (present, absent). Patients in the XALKORI arm received XALKORI 250 mg orally twice daily until documented disease progression, intolerance to therapy, or the investigator determined that the patient was no longer experiencing clinical benefit. Chemotherapy consisted of pemetrexed 500 mg/m² with cisplatin 75 mg/m² or carboplatin AUC of 6 or 5 mg·min·mL⁻¹ by intravenous infusion every 3 weeks for up to 6 cycles. Patients in the chemotherapy arm were not permitted to receive maintenance chemotherapy. At the time of documented disease progression, as per independent radiology review, patients randomized to chemotherapy were offered XALKORI.

The demographic characteristics of the overall study population were 62% female, median age of 53 years, baseline ECOG performance status 0 or 1 (91%), 51% White and 46% Asian, 4% current smokers, 32% past smokers, and 64% never smokers. The disease characteristics of the overall study population were metastatic disease in 98% of patients, 92% of patients’ tumors were classified as adenocarcinoma histology, 27% of patients had brain metastases, and 7% received systemic chemotherapy as adjuvant or neoadjuvant therapy. Of those randomized to chemotherapy, 70% received XALKORI after IRR documented progression.

Study 1 demonstrated a statistically significant improvement in PFS in the patients treated with XALKORI. The OS analysis conducted at the time of the PFS analysis did not suggest a difference in survival between arms. Table 7 and Figure 1 summarize the efficacy results. Exploratory patient-reported symptom measures of baseline and post-treatment dyspnea, cough, and chest pain suggested a delay in time to development of or worsening of dyspnea, but not cough or chest pain, in patients treated with XALKORI as compared to chemotherapy. The patient-reported delay in onset or worsening of dyspnea may be an overestimation, because patients were not blinded to treatment assignment.

#### Table 7. Previously Untreated ALK-Positive Metastatic NSCLC - Efficacy Results

<table>
<thead>
<tr>
<th></th>
<th>XALKORI (N=172)</th>
<th>Chemotherapy (N=171)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Progression-Free Survival (Based on IRR)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Events (%)</td>
<td>100 (58%)</td>
<td>137 (80%)</td>
<td></td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>89 (52%)</td>
<td>132 (77%)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>11 (6%)</td>
<td>5 (3%)</td>
<td></td>
</tr>
<tr>
<td>Median, Months (95% CI)</td>
<td>10.9 (8.3, 13.9)</td>
<td>7.0 (6.8, 8.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Overall Survival</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Events (%)</td>
<td>44 (26%)</td>
<td>46 (27%)</td>
<td></td>
</tr>
<tr>
<td>Median, Months (95% CI)</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.82 (0.54, 1.26)</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td><strong>Tumor Response (Based on IRR)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Objective Response Rate % (95% CI)</td>
<td>74% (67, 81)</td>
<td>45% (37, 53)</td>
<td></td>
</tr>
<tr>
<td>CR, n (%)</td>
<td>3 (1.7%)</td>
<td>2 (1.2%)</td>
<td></td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>125 (73%)</td>
<td>75 (44%)</td>
<td></td>
</tr>
<tr>
<td><strong>Duration of Response</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, Months (95% CI)</td>
<td>11.3 (8.1, 13.8)</td>
<td>5.3 (4.1, 5.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
| HR-hazard ratio: CI-confidence interval; IRR-independent radiology review; NR—not reached; CR-complete response; PR-partial response.
| a Based on the Cox proportional hazards stratified analysis.
| b Based on the stratified log-rank test.
| c OS analysis was not adjusted for the potentially confounding effects of cross over.
| d Based on the stratified cr-Mantel-Haenszel test.

**Figure 1. Kaplan-Meier Curves of Progression-Free Survival as Assessed by IRR in Study 1**

- Based on the stratified log-rank test.
- OS analysis was not adjusted for the potentially confounding effects of cross over.
- Based on the stratified cr-Mantel-Haenszel test.
- Estimated using the Kaplan Meier method.
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><strong>Progression-Free Survival (Based on IRR)</strong></td>
<td></td>
<td></td>
</tr>
<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><strong>Overall Survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Events (%)</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><strong>Tumor Responses (Based on IRR)</strong></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></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Duration of Response</strong></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=independent radiology review; NR=not reached; CR=complete response; PR=partial response;  
A For pemetrexed, the median PFS was 4.2 months. For docetaxel, the median PFS was 2.6 months.  
B Based on the Cox proportional hazards stratified analysis.
C Based on the stratified log-rank test.
D Interim OS analysis conducted at 40% of total events required for final analysis.
E Based on the stratified Cochran-Mantel-Haenszel test.

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 as monotherapy for the treatment of 347 patients with ALK-positive metastatic NSCLC in a phase 1b, multicenter, open-label trial (Study 1) were previously described. Efficacy results are summarized in Table 9.

Table 9. ROS1-Positive Metastatic NSCLC - Efficacy Results

<table>
<thead>
<tr>
<th></th>
<th>IRR (N=50)</th>
<th>Investigator-Assessed (N=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective Response Rate (95% CI)</strong></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 Response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, Months (95% CI)</td>
<td>18.3 (12.7, NR)</td>
<td>14.5 (14.5, NR)</td>
</tr>
</tbody>
</table>
| IRR=independent radiology review; 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 20ºC to 25ºC (68ºF to 77ºF); excursions permitted between 15ºC to 30ºC (59ºF to 86ºF) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

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

Informed consent

Informed 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

Advise 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.

Endocrine-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 90 days after the final dose [see Use in Specific Populations (8.3) and Nonclinical Toxicology (13.1)].

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.
PATIENT INFORMATION
XALKORI® (zal-KOR-ee)
(crizotinib)
capsules

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.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised: March 2016