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----------
Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.5, 5.6) 9/2015

----------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)

----------DOSAGE AND ADMINISTRATION----------
- Recommended dose: 250 mg orally, twice daily (2.2)
- 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)
- 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 with 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)
- Embryofetal 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)

----------ADVERSE REACTIONS----------
The most common adverse reactions (≥25%) are vision disorders, diarrhea, nausea, vomiting, constipation, edema, elevated transaminases, upper respiratory infection, decreased appetite, and dysgeusia. (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*.

----------DRUG INTERACTIONS----------
- CYP3A Inhibitors: 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: 9/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for the treatment of metastatic NSCLC with XALKORI based on the presence of ALK positivity in tumor specimens [see Indications and Usage (1) and Clinical Studies (14)]. Information on FDA-approved tests for the detection of ALK rearrangements in NSCLC is available at ***http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm.***

2.2 Recommended Dosing

The recommended dose of XALKORI is 250 mg orally, twice daily until disease progression or no longer tolerated by the patient. 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 *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

XALKORI may be taken with or without food. Swallow capsules whole. If a dose of XALKORI is missed, make up that dose unless the next dose is due within 6 hours. If vomiting occurs after taking a dose of XALKORI, take the next dose at the regular time.

2.3 Dose Modification

Reduce dose as below, if one or more dose reductions are necessary due to adverse reactions of Grade 3 or 4 severity, as defined by NCI Common Terminology Criteria for Adverse Events (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 once daily

Dose reduction guidelines are provided in Tables 1 and 2.

Table 1. XALKORI Dose Modification – Hematologic Toxicities[a]

CTCAE Grade	XALKORI Dosing
Grade 3	Withhold until recovery to Grade 2 or less, then resume at the same dose schedule
Grade 4	Withhold until recovery to Grade 2 or less, then resume at next lower dose

[a] Except lymphopenia (unless associated with clinical events, e.g., opportunistic infections).

Table 2. XALKORI Dose Modification – Non-Hematologic Toxicities

Criteria	XALKORI Dosing
Alanine aminotransferase (ALT) 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	Withhold until recovery to baseline or less than or equal to 3 times ULN, then resume at reduced dose
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)	Permanently discontinue
Any Grade drug-related interstitial lung disease/pneumonitis	Permanently discontinue
QTc greater than 500 ms on at least 2 separate ECGs	Withhold until recovery to baseline or to a QTc less than 481 ms, then resume at reduced dose
QTc greater than 500 ms or greater than or equal to 60 ms change from baseline with Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	Permanently discontinue
Bradycardia[a] (symptomatic, may be severe and medically significant, medical intervention indicated)	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 anti-hypertensive 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
Bradycardia[a,b] (life-threatening consequences, urgent intervention indicated)	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
Visual Loss (Grade 4 Ocular Disorder)	Discontinue during evaluation of severe vision loss

[a] Heart rate less than 60 beats per minute (bpm).
[b] 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 DOSAGE 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 1669 patients treated with XALKORI across clinical trials in patients with NSCLC. Concurrent elevations in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than or equal to three times the upper limit of normal (ULN) and total bilirubin greater than or equal to two times the ULN, with normal alkaline phosphatase, occurred in 10 patients (0.6%) treated with XALKORI. Additionally, elevations in ALT or AST greater than five times the ULN occurred in 184 (11%) and 93 (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 with liver function tests including ALT 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=1669), 49 XALKORI-treated patients (2.9%) had ILD of any grade, 18 patients (1.1%) had Grade 3 or 4 ILD, and 8 patients (0.5%) had fatal ILD. These cases generally occurred within 3 months after the initiation of XALKORI.

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis. Exclude other potential causes of ILD/pneumonitis, and permanently discontinue XALKORI in patients diagnosed with drug-related ILD/pneumonitis *[see Dosage and Administration (2.3) and Adverse Reactions (6)]*.

5.3 QT Interval Prolongation

QTc prolongation can occur in patients treated with XALKORI. Across clinical trials, 32 of 1560 patients (2.1%) had QTcF (corrected QT by the Fridericia method) greater than or equal to 500 ms and 76 of 1520 patients (5.0%) had an increase from baseline QTcF greater than or equal to 60 ms by automated machine-read evaluation of ECG.

Avoid use of XALKORI in patients with congenital long QT syndrome. Consider periodic monitoring with electrocardiograms (ECGs) and electrolytes in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or who are taking medications that are known to prolong the QT interval. Permanently discontinue XALKORI in patients who develop QTc greater than 500 ms or greater than or equal to 60 ms change from baseline with Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia. Withhold XALKORI in patients who develop QTc greater than 500 ms on at least 2 separate ECGs until recovery to a QTc less than or equal to 480 ms, then resume XALKORI at a reduced dose as described in Table 2 *[see Dosage and Administration (2.3)* and *Clinical Pharmacology (12.2)]*.

5.4 Bradycardia

Symptomatic bradycardia can occur in patients receiving XALKORI. Across clinical trials, bradycardia occurred in 205 (12.3%) of 1669 patients treated with XALKORI. A total of 242 (14.9%) patients had a heart rate less than 50 beats per minute. In Studies 1 and 2, Grade 3 syncope occurred in 2.0% of XALKORI-treated patients and in 0.6% of the chemotherapy-treated patients.

Avoid using XALKORI in combination with other agents known to cause bradycardia (e.g., beta-blockers, non-dihydropyridine calcium channel blockers, clonidine and digoxin) to the extent possible. Monitor heart rate and blood pressure regularly. 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 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% (4/1669). 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 evaluations 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 Embryofetal 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 crizotinib 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)]*.

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 safety of XALKORI is based primarily on 343 patients with ALK-positive metastatic NSCLC who received XALKORI 250 mg twice daily in two open-label, randomized, active-controlled trials (Studies 1 and 2). This is supplemented with information on adverse drug reactions in 1326 patients with ALK-positive metastatic NSCLC who received XALKORI 250 mg twice daily across clinical trials, for a total of 1669 patients across all clinical studies.

The most common adverse reactions (≥25%) of XALKORI in Studies 1 and 2 are vision disorders, diarrhea, nausea, vomiting, constipation, edema, elevated transaminases, upper respiratory infection, decreased appetite, and dysgeusia.

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 who received treatment 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. A total of 169 patients in the chemotherapy arm received pemetrexed 500 mg/m^2 in combination with cisplatin 75 mg/m^2 (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=78). 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 62% 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% 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 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

Adverse Reaction	XALKORI (N=171)		Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) (N=169)	
	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
Cardiac Disorders				
Electrocardiogram QT prolonged	6	2	2	0
Bradycardia[a]	14	1	1	0
Eye Disorders				
Vision disorder[b]	71	1	10	0
Gastrointestinal Disorders				
Vomiting	46	2	36	3
Diarrhea	61	2	13	1
Constipation	43	2	30	0
Dyspepsia	14	0	2	0
Dysphagia	10	1	2	1
Abdominal pain[c]	26	0	12	0
General Disorders and Administration Site Conditions				
Edema[d]	49	1	12	1
Pyrexia	19	0	11	1
Infections and Infestations				
Upper respiratory infection[e]	32	0	12	1
Investigations				
Weight increased	8	1	2	0
Musculoskeletal and Connective Tissue Disorders				
Pain in extremity	16	0	7	0
Muscle spasm	8	0	2	1
Nervous System Disorder				
Dizziness[f]	18	0	10	1
Dysgeusia	26	0	5	0
Headache	22	1	15	0

Includes cases reported within the clustered terms:
[a] Bradycardia (Bradycardia, Sinus bradycardia)
[b] Vision Disorder (Diplopia, Photophobia, Photopsia, Visual acuity reduced, Vision blurred, Vitreous floaters, Visual impairment)
[c] Abdominal pain (Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness)
[d] Edema (Edema, Edema peripheral, Face edema, Generalised edema, Local swelling, Periorbital edema)
[e] Upper respiratory infection (Nasopharyngitis, Pharyngitis, Rhinitis, Upper respiratory tract infection)
[f] Dizziness (Balance disorder, Dizziness, Dizziness postural, Presyncope)

Additional adverse reactions occurring at an overall incidence between 1% and 60% in patients treated with XALKORI included nausea (56%), decreased appetite (30%), fatigue (29%), neuropathy (21%; which included gait disturbance, hypoaesthesia, muscular weakness, neuralgia, neuropathy peripheral, paraesthesia, peripheral sensory neuropathy, polyneuropathy, sensory disturbance), rash (11%), renal cyst (5%), ILD (1%; ILD, pneumonitis), and syncope (1%).

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

Laboratory Abnormality	XALKORI		Chemotherapy	
	Any Grade (%)	Grade 3/4 (%)	Any Grade (%)	Grade 3/4 (%)
Hematology				
Neutropenia	52	11	59	16
Lymphopenia	48	7	53	13
Chemistry				
ALT elevation	79	15	33	2
AST elevation	66	8	28	1
Hypophosphatemia	32	10	21	6

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/m^2 (n=99) or docetaxel 75 mg/m^2 (n=72) by intravenous infusion every three weeks until documented disease progression, intolerance to therapy, or the investigator determined that the patient was no longer experiencing clinical benefit. Patients in the chemotherapy arm received pemetrexed unless they had received pemetrexed as part of first-line or maintenance treatment.

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 (343 received at least one dose of study treatment), the median age was 50 years; 14% of patients were older than 65 years. A total of 56% 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 (3.5%), 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 alanine aminotransferase (ALT) elevation (7.6%) including some patients with concurrent aspartate aminotransferase (AST) elevation, QTc prolongation (2.9%), and neutropenia (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

Adverse Reaction	XALKORI (N=172)		Chemotherapy (Pemetrexed or Docetaxel) (N=171)	
	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
Nervous System Disorder				
Dizziness[a]	22	1	8	0
Dysgeusia	26	0	9	0
Syncope	3	3	0	0
Eye Disorders				
Vision disorder[b]	60	0	9	0
Cardiac Disorders				
Electrocardiogram QT prolonged	5	3	0	0
Bradycardia[c]	5	0	0	0
Investigations				
Weight decreased	10	1	4	0
Gastrointestinal Disorders				
Vomiting	47	1	18	0
Nausea	55	1	37	1
Diarrhea	60	0	19	1
Constipation	42	2	23	0
Dyspepsia	8	0	3	0
Infections and Infestations				
Upper respiratory infection[d]	26	0	13	1
Respiratory, Thoracic and Mediastinal Disorders				
Pulmonary embolism[e]	6	5	2	2
General Disorders and Administration Site Conditions				
Edema[f]	31	0	16	0

Includes cases reported within the clustered terms:
[a] Dizziness (Balance disorder, Dizziness, Dizziness postural)
[b] Vision Disorder (Diplopia, Photophobia, Photopsia, Vision blurred, Visual acuity reduced, Visual impairment, Vitreous floaters)
[c] Bradycardia (Bradycardia, Sinus bradycardia)
[d] Upper respiratory infection (Laryngitis, Nasopharyngitis, Pharyngitis, Rhinitis, Upper respiratory tract infection)
[e] Pulmonary embolism (Pulmonary artery thrombosis, Pulmonary embolism)
[f] Edema (Face edema, Generalized edema, Local swelling, Localized edema, Edema, Edema peripheral, Periorbital edema)

Additional adverse reactions occurring at an overall incidence between 1% and 30% in patients treated with XALKORI included (%), fatigue (27%), neuropathy (19%; dysesthesia, gait disturbance, hypoesthesia, muscular weakness, neuralgia, peripheral neuropathy, parasthesia, peripheral sensory neuropathy, polyneuropathy, burning sensation in skin), rash (9%), ILD (4%; acute respiratory distress syndrome, ILD, pneumonitis), renal cyst (4%), and hepatic failure (1%).

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

Laboratory Abnormality	XALKORI		Chemotherapy	
	Any Grade (%)	Grade 3/4 (%)	Any Grade (%)	Grade 3/4 (%)
Hematology				
Neutropenia	49	12	28	12
Lymphopenia	51	9	60	25
Chemistry				
ALT elevation	76	17	38	4
AST elevation	61	9	33	0
Hypokalemia	18	4	10	1
Hypophosphatemia	28	5	25	6

Description of Selected Adverse Drug Reactions

Vision disorders
Vision disorders, most commonly visual impairment, photopsia, blurred vision, or vitreous floaters, occurred in 1038 (62%) of 1669 patients. The majority (95%) of these patients had Grade 1 visual adverse reactions. 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 (VSAQ-ALK), 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 (>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 (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 419 (25%) of 1669 patients. Most events (95%) were Grade 1 or Grade 2 in severity.

Renal Cysts
Renal cysts were experienced by 50 (3%) of 1669 patients. Renal cysts occurred in 8 (5%) patients treated with XALKORI and 1 (1%) patient treated with chemotherapy in Study 1. Renal cysts occurred in 8 (5%) patients treated with XALKORI and 1 (1%) patient treated with chemotherapy in Study 2. 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.

7 DRUG INTERACTIONS

7.1 Drugs That May Increase Crizotinib Plasma Concentrations

Coadministration of crizotinib with strong CYP3A 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, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, 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 inhibits CYP3A both *in vitro* and *in vivo [see Clinical Pharmacology (12.3)]*. Avoid concomitant use of CYP3A substrates with narrow therapeutic range, including but not limited to alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus in patients taking XALKORI. If concomitant use of these 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.

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 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 2-4% and 15-20%, respectively.

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 breast feed 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 genotoxicty, advise males with females 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 in clinical studies of XALKORI (n=1669), 16% were 65 years or older and 3.7% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and 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 x ULN, or greater than 5 x ULN, if due to liver metastases. Patients with total bilirubin greater than 1.5 x 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 (creatinine clearance [CLcr] 60-89 mL/min) or moderate (CLcr 30-59 mL/min) renal impairment based on a population pharmacokinetic analysis.

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)]*.

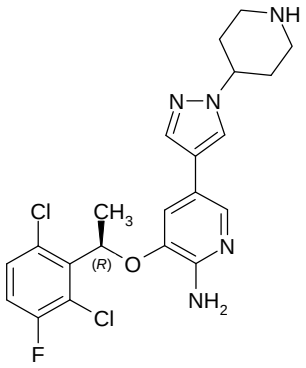
10 OVERDOSAGE

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 $C_{21}H_{22}Cl_2FN_5O$. The molecular weight is 450.34 Daltons. Crizotinib is described chemically as (*R*)-3-[1-(2,6-Dichloro-3-fluorophenyl)ethoxy]-5-[1-(piperidin-4-yl)-1*H*-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 9.4 (piperidinium 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 printed 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, 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 Recepteur d'Origine 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 phosphorylation in cell-based assays using tumor cell lines and demonstrated antitumor activity in mice bearing tumor xenografts that expressed EML4- or NPM-ALK fusion proteins or c-Met.

12.2 Pharmacodynamics

Cardiac Electrophysiology

In an ECG sub-study 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 msec (two-sided 90% upper CI: 19.5 msec). 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 of 4 to 6 hours. Following crizotinib 250 mg twice daily, steady state was reached within 15 days and remained stable, with a median accumulation ratio of 4.8. Steady-state systemic exposure (C_{min} and AUC) appeared to increase in a greater than dose proportional manner over the dose range of 200-300 mg twice daily.

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_{inf} and C_{max} by approximately 14%. XALKORI can be administered with or without food *[see Dosage and Administration (2.2)]*.

Distribution

The geometric mean volume of distribution (Vss) of crizotinib was 1,772 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.

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.

Elimination

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

Following the administration of a single 250 mg radiolabeled 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 2.3% 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 that after a single 250 mg oral dose (100 L/h), which was likely due to autoinhibition of CYP3A by crizotinib after multiple dosing.

Drug interactions

CYP3A inhibitors: Coadministration of a single 150 mg oral dose of crizotinib with ketoconazole (200 mg twice daily), a strong CYP3A inhibitor, increased crizotinib AUC_{inf} and C_{max} values by approximately 3.2-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)]*.

CYP3A inducers: Coadministration of a single 250 mg oral dose of crizotinib with rifampin (600 mg once daily), a strong CYP3A inducer, decreased crizotinib AUC_{inf} and C_{max} by 82% and 69%, respectively, compared to crizotinib alone. However, the magnitude of effect of CYP3A inducers on steady-state crizotinib exposure has not been evaluated *[see Drug Interactions (7.2)]*.

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 (AUC_{inf} decreased by 10% and no change in C_{max}).

CYP3A substrates: Coadministration of crizotinib (250 mg twice daily for 28 days) in patients increased the AUC_{inf} 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, 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, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A 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 UGT1A1, UGT1A4, UGT1A6, UGT1A9 or UGT2B7 are unlikely to occur.

Substrates of transporters: Crizotinib inhibited P-glycoprotein (P-gp) *in vitro* at clinically relevant concentrations. Therefore, crizotinib has the potential to increase plasma concentrations of coadministered drugs that are substrates of P-gp.

Crizotinib inhibited the hepatic uptake transporter, organic cation transporter 1 (OCT1), and renal uptake transporter, organic cation transporter 2 (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 OATP1B1 or OATP1B3, or the renal uptake transport proteins OAT1 or OAT3 *in vitro* at clinically relevant concentrations.

Effect on other transport proteins: Crizotinib did not inhibit the hepatic efflux bile salt export pump transporter (BSEP) *in vitro* at clinically relevant concentrations.

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 x ULN or greater than 5 x ULN if due to liver metastases. Patients with total bilirubin greater than 1.5 x ULN were also excluded *[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 ≥90 mL/min). All patients received a single 250 mg oral dose of XALKORI. The mean AUC_{inf} for crizotinib increased by 79% and the mean C_{max} increased by 34% in patients with severe renal impairment compared to those with normal renal function. Similar changes in AUC_{inf} and C_{max} 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=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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with crizotinib have not been conducted.

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 *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 findings in repeat-dose toxicity studies in the rat. Findings observed in the male reproductive tract included testicular pachytene 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

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 ALK-positive NSCLC as identified by the FDA-approved assay, Vysis ALK Break-Apart FISH Probe Kit, prior to randomization. The major efficacy outcome measure was progression-free survival (PFS) as assessed by independent radiology review (IRR) committee. Additional efficacy outcome measures included objective response rate (ORR) as assessed by IRR, duration of response, 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 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/m^2 with cisplatin 75 mg/m^2 or carboplatin AUC of 5 or 6 mg·min/mL 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 (95%), 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.

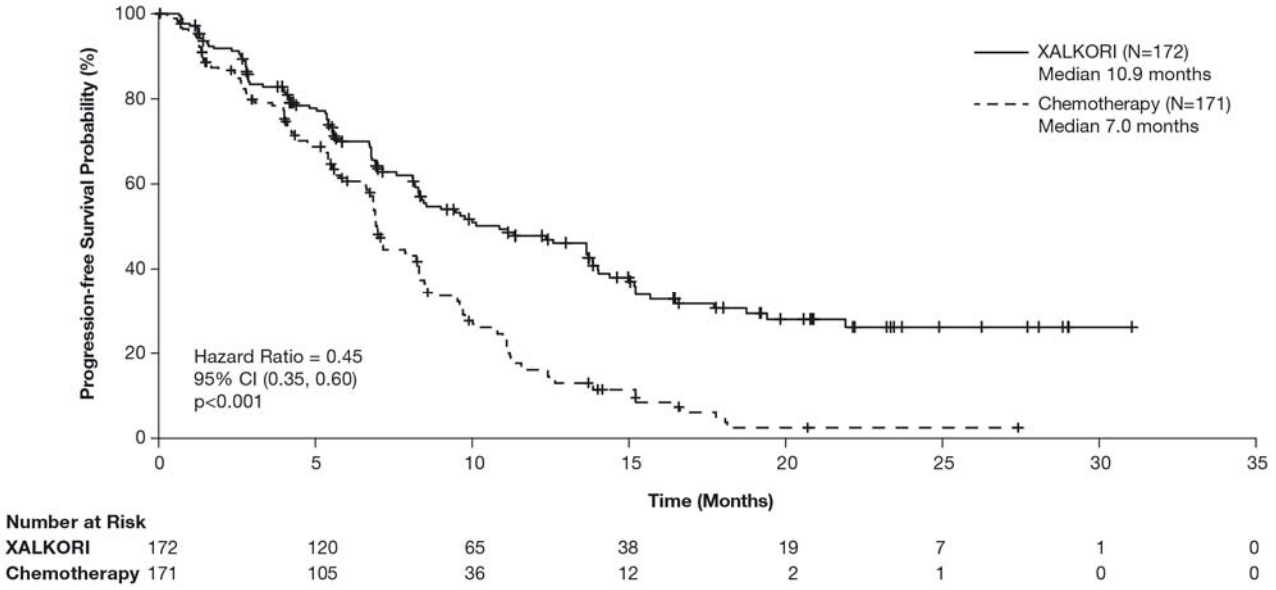
Study 1 demonstrated a statistically significant improvement in PFS in the patients treated with XALKORI. The OS analysis conducted at the time of the PFS analysis did not suggest a difference in survival between arms. Table 7 and Figure 1 summarize the efficacy results. Exploratory patient-reported 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

	XALKORI (N=172)	Chemotherapy (N=171)
Progression-free Survival (Based on IRR)		
Number of Events (%)	100 (58%)	137 (80%)
Progressive Disease	89 (52%)	132 (77%)
Death	11 (6%)	5 (3%)
Median, Months (95% CI)	10.9 (8.3, 13.9)	7.0 (6.8, 8.2)
HR (95% CI)[a]	0.45 (0.35, 0.60)	
P-value[b]	<0.001	
Overall Survival[c]		
Number of Events (%)	44 (26%)	46 (27%)
Median, Months (95% CI)	NR	NR
HR (95% CI)[a]	0.82 (0.54,1.26)	
P-value[b]	0.36	
Tumor Responses (Based on IRR)		
Objective Response Rate % (95% CI)	74% (67, 81)	45% (37, 53)
CR, n (%)	3 (1.7%)	2 (1.2%)
PR, n (%)	125 (73%)	75 (44%)
P-value[d]	<0.001	
Duration of Response		
Median, Months[e] (95% CI)	11.3 (8.1, 13.8)	5.3 (4.1, 5.8)

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 Cochran-Mantel-Haenszel test.
[e] Estimated using the Kaplan Meier method.

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



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 one platinum-based chemotherapy regimen, was demonstrated in a

randomized, multicenter, open-label, active-controlled study (Study 2). The major efficacy outcome was PFS as assessed by IRR. Additional efficacy outcomes included ORR as assessed by IRR, duration of response, 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/m^2 (if pemetrexed naïve; n=99) or docetaxel 75 mg/m^2 (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.

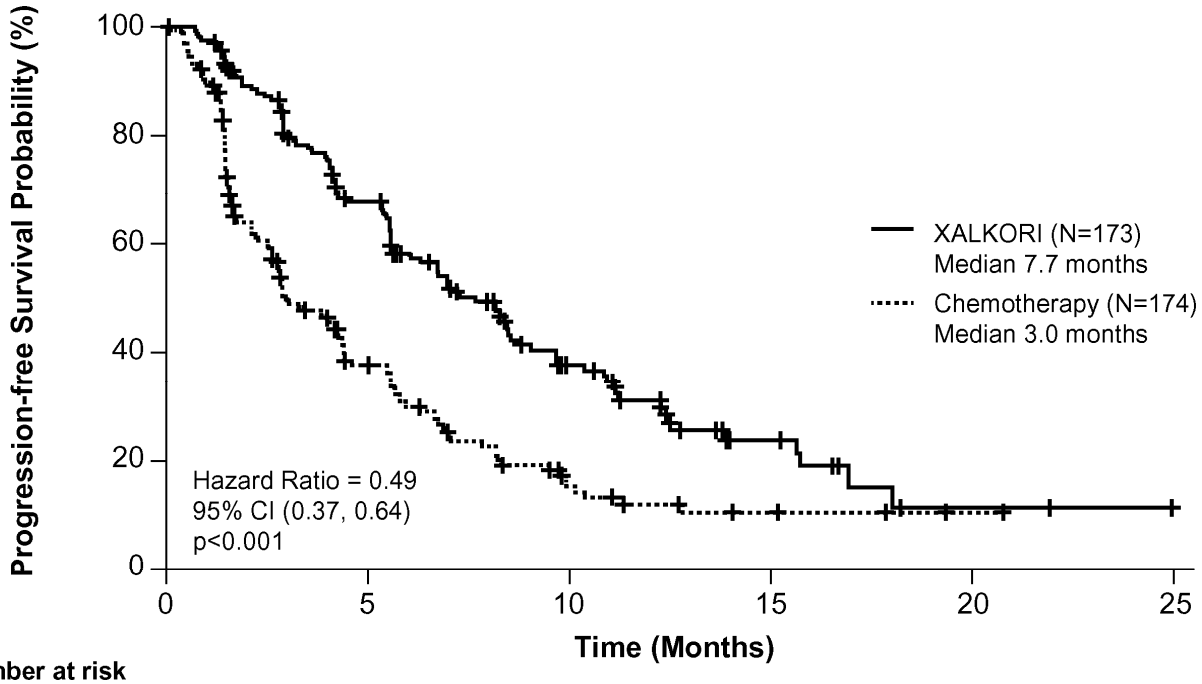
Study 2 demonstrated a statistically significant improvement in PFS in the patients treated with XALKORI. Table 8 and Figure 2 summarize the efficacy results.

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

	XALKORI (N=173)	**Chemotherapy (N=174)**
Progression-free Survival (Based on IRR)		
Number of Events (%)	100 (58%)	127 (73%)
Progressive Disease	84 (49%)	119 (68%)
Death	16 (9%)	8 (5%)
Median, Months (95% CI)	7.7 (6.0, 8.8)	3.0[a] (2.6, 4.3)
HR (95% CI)[b]	0.49 (0.37,0.64)	
P-value[c]	<0.001	
Overall Survival[d]		
Number of Events (%)	49 (28%)	47 (27%)
Median, Months (95% CI)	20.3 (18.1,NR)	22.8 (18.6,NR)
HR (95% CI)[b]	1.02 (0.68,1.54)	
P-value[c]	0.92	
Tumor Responses (Based on IRR)		
Objective Response Rate % (95% CI)	65% (58, 72)	20% (14, 26)
CR, n (%)	1 (0.6%)	0
PR, n (%)	112 (65%)	34 (20%)
P-value[e]	<0.001	
Duration of Response		
Median, Months (95% CI)	7.4 (6.1, 9.7)	5.6 (3.4, 8.3)

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



Number at risk						
XALKORI	173	93	38	11	2	0
Chemotherapy	174	49	15	4	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)*.

- Inform patients of the symptoms of hepatotoxicity, and that they should be reported immediately *[see Warnings and Precautions (5.1)]*.

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

- Inform patients that symptoms of bradycardia including dizziness, lightheadedness, and syncope can occur while taking XALKORI. Advise patients to report these symptoms and to inform their physician about the use of any heart or blood pressure medications *[see Warnings and Precautions (5.4)]*.

- Inform patients of the potential risk of severe visual loss and to immediately contact their physician 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)]*.

- Inform patients that nausea, diarrhea, vomiting, and constipation are the most commonly reported gastrointestinal adverse events occurring in patients who received XALKORI. Nausea and vomiting began most commonly during the first few days of treatment *[see Adverse Reactions (6)]*.

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

- 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.

- 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), 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)]*.

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

- 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)]*.

This product's label may have been updated. For full prescribing information, please visit www.XALKORI.com.

Distributed by
Pfizer Labs
Division of Pfizer Inc, NY, NY 10017

LAB-0440-10.9

PATIENT INFORMATION

XALKORI® (zal-KOR-ee)
(crizotinib)
Capsules

Read this patient information leaflet before you start taking XALKORI and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your condition or treatment.

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 or fatal liver injury. Your doctor should do blood tests at least every month to check your liver while you are taking XALKORI. Tell your doctor right away if you get any of the following:

- your skin or the whites of your eyes turn yellow
- you feel tired
- your urine turns dark or brown (tea color)
- you have nausea or vomiting
- you have a decreased appetite
- you have pain on the right side of your stomach
- you bleed or bruise more easily than normal
- you have itching

Lung problems (pneumonitis). XALKORI may cause life-threatening or fatal swelling (inflammation) of the lungs during treatment. Symptoms may be similar to those symptoms from lung cancer. Tell your doctor right away if you have any new or worsening symptoms, including:

- trouble breathing or shortness of breath
- cough with or without mucous
- fever

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

Vision problems. XALKORI may cause partial or complete loss of vision in one or both eyes. Tell your doctor right away if you have any loss of vision or tell your doctor if you have any change in vision such as difficulty seeing out of one or both eyes. Your doctor may stop XALKORI treatment and refer you to an eye doctor if you develop severe vision problems while taking XALKORI.

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 a gene called ALK (anaplastic lymphoma kinase).

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

What should I tell my doctor before taking XALKORI?

Before you take XALKORI, tell your doctor if you:

- have heart problems, including a condition called long QT syndrome
- have liver or kidney 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 methods of birth control during treatment with XALKORI and for at least 45 days after the last dose of XALKORI. Men who take XALKORI, who have a female partner who can get pregnant, should use birth control during treatment and for at least 90 days after stopping XALKORI.
    - Talk to your doctor about the birth control methods that may be right for you.
    - If you or your partner becomes pregnant, tell your doctor 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. You and your doctor should decide if you will take XALKORI or stop breastfeeding.

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

Know the medicines you take. Keep a list of them to show your doctor or pharmacist when you get a new medicine.

How should I take XALKORI?

- Take XALKORI exactly as your doctor tells you.
- Swallow XALKORI capsules whole.
- You may take XALKORI with or without food.
- Do not change your dose or stop XALKORI unless your doctor 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.
- Call your doctor right away if you take too much XALKORI.
- Your doctor will check your blood and heart while you are taking XALKORI.

What should I avoid while taking XALKORI?

- You should not drink grapefruit juice or eat grapefruit during your treatment with XALKORI. It may make the amount of XALKORI in your blood increase 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. These problems usually happen within 1 week of starting XALKORI. Tell your doctor right away if you have any change in vision, such as double vision, flashes of light, blurred vision, light hurting your eyes, new or increased floaters.
- diarrhea
- nausea
- vomiting
- constipation
- swelling of your hands and feet
- increase in liver enzymes that may indicate liver injury
- upper respiratory infection
- loss of appetite
- taste alteration

Tell your doctor 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 doctor 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 it to other people, even if they have the same symptoms you have. It may harm them. This leaflet provides the most important information about XALKORI. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for more information about

XALKORI that is written for health professionals. For more information, go to **www.XALKORI.com**.

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

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

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