

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, oral
Initial U.S. Approval: August 2011**

-----**INDICATIONS AND USAGE**-----

XALKORI is a kinase inhibitor indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test. (1) This indication is based on response rate. There are no data available demonstrating improvement in patient reported outcomes or survival with XALKORI.

-----**DOSAGE AND ADMINISTRATION**-----

- 250 mg taken orally twice daily with or without food. (2.1)
- Dosing interruption and/or dose reduction to 200 mg taken orally twice daily may be required based on individual safety and tolerability, then to 250 mg taken orally once daily if further reduction is necessary. (2.2)

-----**DOSAGE FORMS AND STRENGTHS**-----

- XALKORI Capsules: 250 mg and 200 mg. (3)

-----**CONTRAINDICATIONS**-----

- None (4)

-----**WARNINGS AND PRECAUTIONS**-----

- **Pneumonitis:** Severe, including fatal, treatment-related pneumonitis has been observed. Monitor patients for pulmonary symptoms indicative of pneumonitis. Permanently discontinue in patients diagnosed with treatment-related pneumonitis. (5.1)
- **Hepatic Laboratory Abnormalities:** Concurrent elevations in ALT and total bilirubin have occurred. Monitor monthly and as clinically indicated with more frequent testing in patients with Grade 2-4

elevations. Temporarily suspend, dose reduce, or permanently discontinue XALKORI as indicated. (5.2)

- **QT Interval Prolongation:** In patients who have a history of or predisposition for QTc prolongation, or who are taking medications that are known to prolong the QT interval, periodic monitoring with electrocardiograms and electrolytes should be considered. (5.3)
- **ALK Testing:** Detection of ALK-positive NSCLC using an FDA-approved test, indicated for this use, is necessary for selection of patients for treatment with XALKORI. (5.4)
- **Pregnancy:** XALKORI can cause fetal harm when administered to a pregnant woman. (5.5, 8.1)

-----**ADVERSE REACTIONS**-----

The most common adverse reactions (≥25%) are vision disorder, nausea, diarrhea, vomiting, edema, and constipation. (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:** Dose reduction may be needed for coadministered drugs that are predominantly metabolized by CYP3A. Avoid concurrent use of XALKORI with CYP3A substrates with narrow therapeutic indices. (7.3)

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

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FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

XALKORI is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (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.

2. DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The recommended dose and schedule of XALKORI is 250 mg taken orally twice daily. Continue treatment as long as the patient is deriving clinical benefit from therapy. Capsules should be swallowed whole. XALKORI may be taken with or without food. If a dose of XALKORI is missed, then it should be taken as soon as the patient remembers unless it is less than 6 hours until the next dose, in which case the patient should not take the missed dose. Patients should not take 2 doses at the same time to make up for a missed dose.

2.2 Dose Modification

Dosing interruption and/or dose reduction may be required based on individual safety and tolerability. If dose reduction is necessary, then the dose of XALKORI should be reduced to 200 mg taken orally twice daily. If further dose reduction is necessary, then reduce the dosage to 250 mg taken orally once daily based on individual safety and tolerability. Dose reduction guidelines for hematologic and non-hematologic toxicities are provided in Tables 1 and 2.

Table 1: XALKORI Dose Modification – Hematologic Toxicities^a

CTCAE ^b Grade	XALKORI Dosing
Grade 3	Withhold until recovery to Grade ≤ 2 , then resume at the same dose schedule
Grade 4	Withhold until recovery to Grade ≤ 2 , then resume at 200 mg twice daily ^c

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

^b NCI Common Terminology Criteria for Adverse Events.

^c In case of recurrence, withhold until recovery to Grade ≤ 2 , then resume at 250 mg once daily. Permanently discontinue in case of Grade 4 recurrence.

Table 2: XALKORI Dose Modification – Non-Hematologic Toxicities

CTCAE Grade	XALKORI Dosing
Grade 3 or 4 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation with Grade \leq 1 total bilirubin	Withhold until recovery to Grade \leq 1 or baseline, then resume at 200 mg twice daily ^a
Grade 2, 3 or 4 ALT or AST elevation with concurrent Grade 2, 3 or 4 total bilirubin elevation (in the absence of cholestasis or hemolysis)	Permanently discontinue
Any Grade pneumonitis ^b	Permanently discontinue
Grade 3 QTc prolongation	Withhold until recovery to Grade \leq 1, then resume at 200 mg twice daily ^a
Grade 4 QTc prolongation	Permanently discontinue

^a In case of recurrence, withhold until recovery to Grade \leq 1, then resume at 250 mg once daily. Permanently discontinue in case of further Grade 3 or 4 recurrence.

^b Not attributable to NSCLC progression, other pulmonary disease, infection, or radiation effect.

Complete blood counts including differential white blood cell counts should be monitored monthly and as clinically indicated, with more frequent repeat testing if Grade 3 or 4 abnormalities are observed, or if fever or infection occurs. Liver function tests should be monitored monthly and as clinically indicated, with more frequent repeat testing if Grade 2, 3 or 4 abnormalities are observed.

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 Pneumonitis

XALKORI has been associated with severe, life-threatening, or fatal treatment-related pneumonitis in clinical trials with a frequency of 4 in 255 (1.6%) patients across Studies A and B. All of these cases occurred within 2 months after the initiation of treatment. Patients should be monitored for pulmonary symptoms indicative of pneumonitis. Other causes of pneumonitis should be excluded. XALKORI should be permanently discontinued in patients diagnosed with treatment-related pneumonitis [*see Dosage and Administration (2.2)*].

5.2 Hepatic Laboratory Abnormalities

Grade 3 or 4 ALT elevation was observed in 7% of patients in Study A and in 4% of patients in Study B. Grade 3 and 4 elevations were generally asymptomatic and reversible upon dosing interruption. Patients usually resumed treatment at a lower dose without recurrence; however, 3 patients from Study A (2%) and 1 patient from Study B (less than 1%) required permanent discontinuation from treatment. Concurrent elevations in ALT greater than 3 x ULN and total bilirubin greater than 2 x ULN without elevated alkaline phosphatase were detected in 1/255 (less than 0.5%) of patients with available laboratory data across both studies. Liver function tests including ALT and total bilirubin should be monitored once a month and as clinically indicated, with more

frequent repeat testing for Grades 2, 3 or 4 elevation in patients who develop transaminase elevations [see *Dosage and Administration (2.2) and Adverse Reactions (6)*].

5.3 QT Interval Prolongation

QTc prolongation has been observed. XALKORI should be avoided in patients with congenital long QT syndrome. In patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or who are taking medications that are known to prolong the QT interval, periodic monitoring with electrocardiograms (ECGs) and electrolytes should be considered. Permanently discontinue XALKORI in patients who develop Grade 4 QTc prolongation. Withhold XALKORI in patients who develop Grade 3 QTc prolongation until recovery to less than or equal to Grade 1, then resume XALKORI at 200 mg twice daily. In case of recurrence of Grade 3 QTc prolongation, withhold XALKORI until recovery to less than or equal to Grade 1, then resume XALKORI at 250 mg once daily. Permanently discontinue XALKORI if Grade 3 QTc prolongation recurs [see *Dosage and Administration (2.2) and Clinical Pharmacology (12.4)*].

5.4 ALK Testing

Detection of ALK-positive NSCLC using an FDA-approved test, indicated for this use, is necessary for selection of patients for treatment with XALKORI [see *Clinical Studies (14)*].

Assessment for ALK-positive NSCLC should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. Improper assay performance can lead to unreliable test results.

Refer to an FDA-approved test's package insert for instructions on the identification of patients eligible for treatment with XALKORI.

5.5 Pregnancy

XALKORI can cause fetal harm when administered to a pregnant woman based on its mechanism of action. In nonclinical studies in rats, crizotinib was embryotoxic and fetotoxic at exposures similar to and above those observed in humans at the recommended clinical dose of 250 mg twice daily. There are no adequate and well-controlled studies in pregnant women using XALKORI. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus [see *Use in Specific Populations (8.1)*].

6. ADVERSE REACTIONS

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 practice.

In Studies A and B, patients with locally advanced or metastatic ALK-positive NSCLC received crizotinib 250 mg orally twice daily continuously. Among the 255 patients for whom data on Grade 1-4 adverse reactions are available, median exposure to study drug was 5.1 months in Study A and 7.8 months in Study B. Dosing interruptions occurred in 36% and 45% of patients in Studies A and B, and lasted greater than 2 weeks in 13% and 19% of patients in Studies A and B, respectively. Dose reductions occurred in 44% and 29% of patients in Studies A and B, respectively. The rates of treatment-related adverse events resulting in permanent discontinuation were 6% in Study A and 3% in Study B. The most common adverse reactions ($\geq 25\%$) across both studies were vision disorder, nausea, diarrhea, vomiting, edema, and constipation. Grade 3-4 adverse reactions in at least 4% of patients in both studies included ALT increased and neutropenia.

Among the 397 patients for whom information on deaths and serious adverse reactions are available, deaths within 28 days of the last dose of study drug occurred in 45 patients. Ten (2.5%) patients died within 28 days of their first dose of study drug. Causes of death included disease progression (32 patients), respiratory events (9), and other (4). Respiratory causes of death included pneumonia (2), hypoxia (2), ARDS (1), dyspnea (1), pneumonitis (1), empyema (1), and pulmonary hemorrhage (1). Other causes of deaths included septic shock,

DIC, cardiovascular event, and death due to unknown cause (1 each). Serious adverse events in greater than or equal to 2% of patients included pneumonia, dyspnea, and pulmonary embolism.

Table 3 lists the common adverse reactions on Studies A and B in patients receiving XALKORI.

Table 3: Adverse Reactions in ≥10% of Patients with Locally Advanced or Metastatic ALK-Positive NSCLC on Studies A and B¹

Adverse Event	Treatment Emergent N=255		Treatment Related N=255	
	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Eye Disorders				
Vision Disorder ²	163 (64%)	0	159 (62%)	0
Gastrointestinal Disorders				
Nausea	145 (57%)	2 (<1%)	136 (53%)	0
Diarrhea	124 (49%)	1 (<1%)	109 (43%)	0
Vomiting	116 (45%)	3 (1%)	101 (40%)	0
Constipation	98 (38%)	2 (<1%)	69 (27%)	1 (<1%)
Esophageal Disorder ³	51 (20%)	3 (1%)	29 (11%)	0
Abdominal Pain ⁴	40 (16%)	1 (<1%)	20 (8%)	0
Stomatitis ⁵	27 (11%)	1 (<1%)	15 (6%)	1 (<1%)
General Disorders				
Edema ⁶	97 (38%)	2 (<1%)	72 (28%)	0
Fatigue	80 (31%)	6 (2%)	51 (20%)	4 (2%)
Chest Pain/Discomfort ⁷	30 (12%)	1 (<1%)	3 (1%)	0
Fever	30 (12%)	1 (<1%)	2 (<1%)	0
Infections and Infestations				
Upper Respiratory Infection ⁸	50 (20%)	1 (<1%)	4 (2%)	0
Investigations				
Alanine Aminotransferase Increased	38 (15%)	17 (7%)	34 (13%)	14 (5%)
Aspartate Aminotransferase Increased	29 (11%)	7 (3%)	24 (9%)	5 (2%)
Metabolism and Nutrition				
Decreased Appetite	69 (27%)	3 (1%)	49 (19%)	0
Musculoskeletal				
Arthralgia	29 (11%)	3 (1%)	4 (2%)	0
Back Pain	28 (11%)	0	2 (<1%)	0
Nervous System Disorders				
Dizziness ⁹	60 (24%)	0	42 (16%)	0
Neuropathy ¹⁰	58 (23%)	1 (<1%)	34 (13%)	1 (<1%)
Headache	34 (13%)	1 (<1%)	10 (4%)	0
Dysgeusia	33 (13%)	0	30 (12%)	0
Psychiatric Disorders				
Insomnia	30 (12%)	0	8 (3%)	0
Respiratory Disorders				
Dyspnea	57 (22%)	16 (6%)	5 (2%)	3 (1%)
Cough	54 (21%)	3 (1%)	9 (4%)	0
Skin Disorders				
Rash	41 (16%)	0	25 (10%)	0

¹Study A used CTCAE v4.0, and Study B used CTCAE v3.0.

²Includes diplopia, photopsia, photophobia, vision blurred, visual field defect, visual impairment, vitreous floaters, visual brightness, and visual acuity reduced.

³Includes dyspepsia, dysphagia, epigastric discomfort/pain/burning, esophagitis, esophageal obstruction/pain/spasm/ulcer, gastroesophageal reflux, odynophagia, and reflux esophagitis.

⁴Includes abdominal discomfort, abdominal pain, abdominal pain upper, and abdominal tenderness.

⁵Includes mouth ulceration, glossodynia, glossitis, cheilitis, mucosal inflammation, oropharyngeal pain/discomfort, oral pain, and stomatitis.

⁶Includes edema, edema localized, and peripheral edema.

⁷Includes chest pain, chest discomfort, and musculoskeletal chest pain.

⁸Includes nasopharyngitis, rhinitis, pharyngitis, and upper respiratory tract infection.

⁹Includes balance disorder, dizziness, and presyncope.

¹⁰Includes burning sensation, dysesthesia, hyperesthesia, hypoesthesia, neuralgia, paresthesia, peripheral neuropathy, peripheral motor neuropathy, and peripheral sensory neuropathy.

Vision disorders including visual impairment, photopsia, vision blurred, vitreous floaters, photophobia, and diplopia were reported in 159 (62%) patients in clinical trials. These events generally started within two weeks of drug administration. Ophthalmological evaluation should be considered, particularly if patients experience photopsia or experience new or increased vitreous floaters. Severe or worsening vitreous floaters and/or photopsia could also be signs of a retinal hole or pending retinal detachment. Caution should be exercised when driving or operating machinery by patients who experience vision disorder [*see Patient Counseling Information (17)*].

Neuropathy as defined in Table 3 and attributed to study drug by the investigator was reported in 34 (13%) patients. While most events were Grade 1, Grade 2 motor neuropathy and Grade 3 peripheral neuropathy were reported in 1 patient each. Dizziness and dysgeusia were also very commonly reported in these studies, but were all Grade 1 or 2 in severity.

Bradycardia has been reported in 12 (5%) patients treated with XALKORI. All of these cases were Grade 1 or 2 in severity.

Complex renal cysts have been reported in 2 (1%) patients treated with XALKORI. There were no reports of abnormal urinalyses or renal impairment in these cases.

Laboratory Abnormalities

Grade 3 or 4 neutropenia, thrombocytopenia, and lymphopenia were seen in 5.2%, 0.4%, and 11.4% of patients, respectively.

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)*]. The concomitant use of strong CYP3A inhibitors, including but not limited to atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, and voriconazole, should be avoided. Grapefruit or grapefruit juice may also increase plasma concentrations of crizotinib and should be avoided. Caution should be exercised 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)*]. The concurrent use of strong CYP3A inducers, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's Wort, should be avoided.

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)*]. Dose reduction may be needed for coadministered drugs that are predominantly metabolized by CYP3A. Coadministration of crizotinib with CYP3A substrates with narrow therapeutic indices, including but not limited to alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozone, quinidine, sirolimus, and tacrolimus, should be avoided.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D [see “Warnings and Precautions” (5.5)]

XALKORI can cause fetal harm when administered to a pregnant woman based on its mechanism of action. There are no adequate and well-controlled studies of XALKORI in pregnant women. In nonclinical studies in rats, crizotinib was embryotoxic and fetotoxic at exposures similar to and above those observed in humans at the recommended clinical dose of 250 mg twice daily. 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 1.2 times the AUC at the recommended human dose) in rats. No teratogenic effects were observed in rats at doses up to the maternally toxic dose of 200 mg/kg/day (approximately 5 times the AUC at the recommended human dose) or in rabbits at doses of up to 60 mg/kg/day (approximately 3 times the AUC at the recommended human dose), though fetal body weights were reduced at these doses.

Women of childbearing potential should be advised to avoid becoming pregnant while receiving XALKORI. Women of childbearing potential who are receiving this drug, or partners of women of childbearing potential receiving this drug, should use adequate contraceptive methods during therapy and for at least 90 days after completing therapy. If this drug is used during pregnancy, or if the patient or their partner becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

8.3 Nursing Mothers

It is not known whether XALKORI is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from XALKORI, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and efficacy of XALKORI in pediatric patients has not been established. 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 10 times the AUC in adult patients at the recommended human dose). Other toxicities of potential concern to pediatric patients have not been evaluated in juvenile animals.

8.5 Geriatric Use

Of the 119 patients in Study A, 16 (13%) were 65 years or older. Of the 136 patients in Study B, 19 (14%) were 65 years or older. No overall differences in safety or efficacy were observed in comparison with 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. Treatment with XALKORI should be used with 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 [CL_{Cr}] 60 to 90 mL/min) and moderate renal impairment (CL_{Cr} 30 to 60 mL/min), as steady-state trough concentrations in these two groups were similar to those in patients with normal renal function (CL_{Cr} greater than 90 mL/min) in Study B. The potential need for starting dose adjustment in patients with severe renal impairment cannot be determined, as clinical and pharmacokinetic data were available for only one patient. In addition, no data are available for patients with end-stage renal disease. Therefore, caution should be used in patients with severe renal

impairment (CLcr less than 30 mL/min) or patients with end-stage renal disease [see *Clinical Pharmacology (12.3)*].

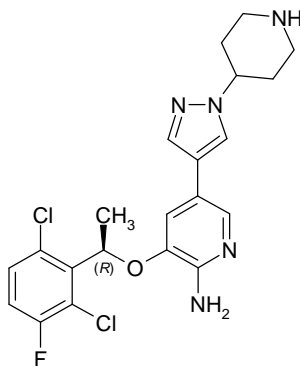
10. OVERDOSAGE

There have been no known cases of XALKORI overdose. Treatment of overdose with XALKORI should consist of general supportive measures. 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), 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 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.

12.3 Pharmacokinetics

Absorption

Following oral single-dose administration, 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 the administration of 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 (2.1)*].

Distribution

The geometric mean volume of distribution (V_{ss}) 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

In vitro studies demonstrated that 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.

In vitro studies in human liver microsomes demonstrated that crizotinib is a time-dependent inhibitor of CYP3A.

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/hr) after 250 mg twice daily than that after a single 250 mg oral dose (100 L/hr), which was likely due to autoinhibition of CYP3A by crizotinib after multiple dosing.

Drug Interactions

Coadministration of Crizotinib and CYP3A Substrates

Crizotinib inhibits CYP3A both *in vitro* and *in vivo*. Coadministration of crizotinib (250 mg twice daily for 28 days) in patients resulted in a geometric mean oral midazolam AUC that was 3.7-fold that observed when midazolam was administered alone, suggesting that crizotinib is a moderate inhibitor of CYP3A [*see Drug Interactions (7.3)*].

Coadministration of Crizotinib and CYP3A Inhibitors

Coadministration of a single 150 mg oral dose of crizotinib in the presence of ketoconazole (200 mg twice daily), a strong CYP3A inhibitor, resulted in increases in crizotinib systemic exposure, with crizotinib AUC_{inf}

and C_{\max} values that were approximately 3.2-fold and 1.4-fold, respectively, those seen when crizotinib was administered alone. However, the magnitude of effect of CYP3A inhibitors on steady-state crizotinib exposure has not been evaluated [see *Drug Interactions (7.1)*].

Coadministration of Crizotinib and CYP3A Inducers

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

Coadministration of Crizotinib and Antacids

The aqueous solubility of crizotinib is pH dependent, with higher pH resulting in lower solubility. Drugs that elevate the gastric pH (such as proton pump inhibitors, H_2 blockers, or antacids) may decrease the solubility of crizotinib and subsequently reduce its bioavailability. However, no formal studies have been conducted.

Coadministration With Other CYP Substrates

In vitro studies indicated that clinical drug-drug interactions are unlikely to occur as a result of crizotinib-mediated inhibition of the metabolism of substrates for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6.

An *in vitro* study in human hepatocytes indicated that clinical drug-drug interactions are unlikely to occur as a result of crizotinib-mediated induction of the metabolism of substrates for CYP1A2 or CYP3A.

Coadministration With Substrates of Transporters

Crizotinib is an inhibitor of P-glycoprotein (P-gp) *in vitro*. Therefore, crizotinib may have the potential to increase plasma concentrations of coadministered substrates of P-gp.

In vitro, crizotinib did not inhibit the human hepatic uptake transport proteins OATP1B1 or OATP1B3 at therapeutic concentrations. Therefore, clinical drug-drug interactions are unlikely to occur as a result of crizotinib-mediated inhibition of the hepatic uptake of substrates for these transporters.

Pharmacokinetics in Special 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)*].

Renal Impairment: No dedicated renal impairment trial for XALKORI has been conducted. In Study B, steady-state trough concentrations in patients with mild (CL_{cr} 60 to 90 mL/min, N=47) and moderate renal impairment (CL_{cr} 30 to 60 mL/min, N=27) were similar to those in patients with normal renal function (CL_{cr} greater than 90 mL/min, N=33). Limited data (N=1) are available in patients with severe renal impairment, and no data are available in patients with end-stage renal disease [see *Use in Specific Populations (8.7)*].

Ethnicity: After 250 mg twice daily dosing, steady-state crizotinib C_{\max} and AUC_{τ} in Asian patients were 1.57- and 1.50-fold those seen in non-Asian patients, respectively.

12.4 Cardiac Electrophysiology

The QT interval prolongation potential of crizotinib was assessed in all patients who received XALKORI 250 mg twice daily. Serial ECGs in triplicate were collected following a single dose and at steady state to evaluate the effect of crizotinib on QT intervals. Four of 308 patients (1.3%) were found to have QTcF (corrected QT by the Fridericia method) greater than or equal to 500 msec, and 10 of 289 patients (3.5%) had an increase from

baseline QTcF greater than or equal to 60 msec by automated machine-read evaluation of ECG. A pharmacokinetic/pharmacodynamic analysis suggested a concentration-dependent increase in QTcF [see *Warnings and Precautions (5.3)*].

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 3 times the AUC at the recommended human dose). 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 daily dose on a mg/m² basis) for 3 days.

14. CLINICAL STUDIES

The use of single-agent XALKORI in the treatment of locally advanced or metastatic ALK-positive NSCLC was investigated in 2 multi-center, single-arm studies (Studies A and B). Patients enrolled into these studies had received prior systemic therapy, with the exception of 15 patients in Study B who had no prior systemic treatment for locally advanced or metastatic disease. In Study A, ALK-positive NSCLC was identified using the Vysis ALK Break-Apart FISH Probe Kit. In Study B, ALK-positive NSCLC was identified using a number of local clinical trial assays. The primary efficacy endpoint in both studies was Objective Response Rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST). Response was evaluated by the investigator and by an independent radiology review panel. Duration of Response (DR) was also evaluated. Patients received 250 mg of XALKORI orally twice daily. Demographic and disease characteristics for Studies A and B are provided in Table 4.

Table 4: Demographic and Disease Characteristics in Studies A and B

Characteristics	Study A N=136	Study B N=119
Sex, n (%)		
Male	64 (47)	59 (50)
Female	72 (53)	60 (50)
Age (years)		
Median (range)	52 (29-82)	51 (21-79)
Race, n (%)		
White	87 (64)	74 (62)
Black	5 (4)	3 (3)
Asian	43 (32)	34 (29)
Other	1 (1)	8 (7)
ECOG PS at baseline, n (%)		
0	37 (27)	41 (35)
1	74 (54)	63 (53)
2 – 3 ^a	25 (18)	15 (13)
Smoking status, n (%)		
Never smoked	92 (68)	86 (72)
Former smoker	39 (29)	32 (27)
Current smoker	5 (4)	1 (1)
Disease stage, n (%)		
Locally advanced	9 (7)	5 (4)
Metastatic	127 (93)	114 (96)
Histological classification, n (%)		
Adenocarcinoma	130 (96)	116 (98)
Large cell carcinoma	1 (1)	1 (1)
Squamous cell carcinoma	0	1 (1)
Adenosquamous carcinoma	3 (2)	0
Other	2 (2)	1 (1)
Prior systemic therapy for locally advanced or metastatic disease -- number of regimens, n (%)		
0	0	15 (13)
1	13 (10)	34 (29)
2	37 (27)	20 (17)
3	37 (27)	17 (14)
≥4	49 (36)	33 (28)

^a Includes 1 patient with an ECOG PS of 1 at screening but was 3 at baseline.

One hundred thirty-six patients with locally advanced or metastatic ALK-positive NSCLC from Study A were analyzed at the time of data cutoff. The median duration of treatment was 22 weeks. Based on investigator assessments, there was 1 complete and 67 partial responses for an ORR of 50% (95% CI: 42%, 59%). Seventy-nine percent of objective tumor responses were achieved during the first 8 weeks of treatment. The median response duration was 41.9 weeks.

One hundred nineteen patients with locally advanced or metastatic ALK-positive NSCLC were enrolled into Study B at the time of data cutoff. The median duration of treatment was 32 weeks. Based on investigator assessments, there were 2 complete and 69 partial responses for an ORR of 61% (95% CI: 52%, 70%). Fifty-five percent of objective tumor responses were achieved during the first 8 weeks of treatment. The median response duration was 48.1 weeks.

Efficacy data from Studies A and B are provided in Table 5.

**Table 5: Locally Advanced or Metastatic ALK-Positive NSCLC
Efficacy Results from Studies A and B^a**

Efficacy Parameter	Study A N=136	Study B N=119
ORR (CR+PR) ^b [% (95% CI)]	50% (42%, 59%)	61% (52%, 70%)
Number of Responders	68	71
Duration of Response ^c [Median (range) weeks]	41.9 (6.1+, 42.1+)	48.1 (4.1+, 76.6+)

^aResponse as assessed by the Investigator.

^bOne patient was not evaluable for response in Study A; 3 patients were not evaluable for response in Study B.

^cPreliminary estimate using Kaplan-Meier method.

+Censored values

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

See 17.7 for FDA-Approved Patient Labeling.

17.1 Gastrointestinal Effects

Patients should be informed that nausea, diarrhea, vomiting, and constipation were the most commonly reported gastrointestinal adverse events occurring in patients who received XALKORI. Supportive care for gastrointestinal adverse events requiring treatment may include standard anti-emetic and/or anti-diarrheal or laxative medications [see Adverse Reactions (6)].

17.2 Visual Effects

Patients should be informed that visual changes such as perceived flashes of light, blurry vision, light sensitivity, and floaters were commonly reported adverse events. These events began most commonly during the first two weeks of treatment. Patients should be advised to report flashes or floaters to their physicians [see Adverse Reactions (6)].

17.3 Effects on Ability to Drive and Use Machines

No studies on the effect of XALKORI on the ability to drive and use machines have been performed. However, caution should be exercised when driving or operating machinery by patients who experience vision disorder, dizziness, or fatigue while taking XALKORI [see Adverse Reactions (6)].

17.4 Concomitant Medications

Patients should be advised 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)].

17.5 Instructions for Taking XALKORI

Patients should be advised to take XALKORI exactly as prescribed, not to change their dose or to stop taking XALKORI unless they are told to do so by their doctor. XALKORI may be taken with or without food. XALKORI capsules should be swallowed whole.

Patients should be instructed to keep XALKORI in the original container. Patients should not crush, dissolve, or open capsules.

Patients should avoid grapefruit or grapefruit juice while taking XALKORI.

If a patient misses a dose, the patient should be advised to take it as soon as they remember unless it is less than 6 hours until the next dose, in which case they should not take the missed dose. Patients should not take 2 doses at the same time to make up for a missed dose.

17.6 Pregnancy and Nursing

Patients of childbearing potential must be told to use adequate contraceptive methods during therapy and for at least 90 days after completing therapy. Patients should be advised to inform their doctor if they or their partners are pregnant or think they may be pregnant. Patients should also be advised not to breastfeed while taking XALKORI.

17.7 FDA-Approved Patient Labeling

LAB-0440-2.0

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 for me to know about XALKORI?

XALKORI may cause serious side effects, such as:

Swelling of the lungs (pneumonitis) - XALKORI may cause life-threatening 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

Liver problems - Your doctor should do blood tests 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

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 is advanced or 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 may harm your unborn baby.
 - Women who are able to become pregnant and men who take XALKORI should use birth control during treatment and for 3 months 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. You and your doctor should decide if you will take XALKORI or breastfeed. You should not do both.

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

Especially tell your doctor if you take:

- St. John's Wort (*Hypericum perforatum*)

- Medicines for:
 - depression (antidepressants)
 - fungal infections (antifungals)
 - bacterial infections (antibiotics)
 - tuberculosis (TB)
 - HIV-AIDS
 - heart conditions
 - seizures

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.
- Do not crush, dissolve, or open capsules.
- 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.
- Do not take more than 1 dose of XALKORI at a 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, use caution when 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:

- **See “What is most important for me to know about XALKORI?”**
- Changes in your heartbeat (called QT interval prolongation), very fast or abnormal heartbeats. Your doctor may check your heart during treatment with XALKORI. Tell your doctor right away if you have abnormal heartbeats, feel dizzy, or faint. These may be symptoms related to QT interval prolongation.

The most common side effects of XALKORI include:

- Vision problems
- These problems usually happen within 2 weeks of starting XALKORI. Tell your doctor right away if you have any change in vision, such as:
 - flashes of light
 - blurred vision
 - light hurting your eyes
 - new or increased floaters
- nausea
- diarrhea
- vomiting
- swelling of your hands and feet
- constipation

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 do I store XALKORI?

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

- Keep XALKORI in the original container, and keep the container closed tightly.
- Do not touch or handle crushed or broken XALKORI capsules. XALKORI is made with a capsule to prevent contact with the active ingredient.

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 to know more about XALKORI talk with your doctor. You can ask your doctor or pharmacist for more information about XALKORI.

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.

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