The format of this leaflet was determined by the Ministry of Health and its content was checked and approved

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.

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. 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.

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 reduce the dose of XALKORI 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 further 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 ≤1 total bilirubin	Withhold until recovery to Grade ≤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 ≤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 ≤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.

Monitor 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. Monitor liver function tests monthly and as clinically indicated, with more frequent repeat testing if Grade 2, 3 or 4 abnormalities are observed.

3. DOSAGE FORMS AND STRENGTHS

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.

250 mg capsules

Hard gelatin capsule, size 0, pink opaque cap and body, with “Pfizer” on the cap and “CRZ 250” on the body.

4. CONTRAINDICATIONS

None

5. WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity

Drug-induced hepatotoxicity with fatal outcome has occurred. These cases have occurred during XALKORI treatment in less than 1% of patients in clinical trials. Concurrent elevations in ALT greater than 3 times the upper limit of normal and total bilirubin greater than 2 times the upper limit of normal, with normal alkaline phosphatase , occurred in less than 1% of patients in clinical trials. Elevation in ALT greater than 5 times the upper limit of normal occurred in 7% of patients in Study A and in 4% of patients in Study B. These laboratory findings 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. Transaminase elevations generally occurred within the first 2 months of treatment. Monitor with liver function tests including ALT and total bilirubin once a month and as clinically indicated, with more frequent repeat testing for increased liver transaminases, alkaline phosphatase, or total bilirubinin patients who develop transaminase elevations *[see Dosage and Administration (2.2) and Adverse Reactions (6)]*.

5.2 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. Monitor patients for pulmonary symptoms indicative of pneumonitis. Exclude other causes of pneumonitis , and permanently discontinue XALKORI in patients diagnosed with treatment-related pneumonitis *[see Dosage and Administration (2.2)]*.

5.3 QT Interval Prolongation

QTc prolongation has been observed. 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 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. Female patients taking crizotinib during pregnancy or who become pregnant while taking crizotinib should be apprised of the potential hazard to a fetus. Male patients taking crizotinib should also be apprised of the potential hazard to a fetus if their partner is or should become pregnant. *[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 (≥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 is 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 B[1]

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

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

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

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

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

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

[6]Includes edema, edema localized, and peripheral edema.

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

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

[9]Includes balance disorder, dizziness, and presyncope.

[10]Includes 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. Consider ophthalmological evaluation, 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. Advise patients to exercise caution when driving or operating machinery due to the risk of developing a 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 occurredin 12 (5%) patients treated with XALKORI. All of these cases were Grade 1 or 2 in severity.

Complex renal cysts occurredin 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 occurredin 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)]*. 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 concurrent 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)]*. Dose reduction may be needed for coadministered drugs that are predominantly metabolized by CYP3A. Avoid coadministration of crizotinib with CYP3A substrates with narrow therapeutic indices, including but not limited to alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus.

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.

Advise women of childbearing potential 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, apprise the patient 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, consider 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

Clinical studies of XALKORI did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently from younger patients. 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.

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 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 [CLcr] 60 to 90 mL/min) and moderate renal impairment (CLcr 30 to 60 mL/min), as steady-state trough concentrations in these two groups were similar to those in patients with normal renal function (CLcr 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, use caution in patients with severe renal impairment (CLcr less than 30 mL/min) or patients with end-stage renal disease *[see Clinical Pharmacology (12.3)]*.

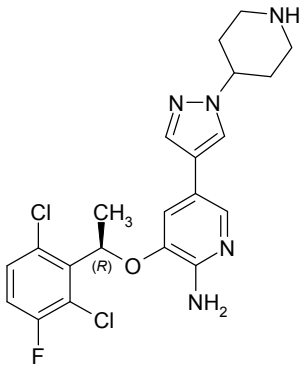
10. OVERDOSAGE

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 (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

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 (CLcr 60 to 90 mL/min, N=47) and moderate renal impairment

(CLcr 30 to 60 mL/min, N=27) were similar to those in patients with normal renal function (CLcr 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/m^2 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**
Objective Response Rate (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+)

[a]Response as assessed by the Investigator.

[b]One patient was not evaluable for response in Study A; 3 patients were not evaluable for response in Study B.

[c]Preliminary 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 or cartons of 60 capsules

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 or cartons of 60 capsules

Store below 25°C

After first opening, use within one month.

17. PATIENT COUNSELING INFORMATION

17.1 Hepatotoxicity

Inform patients that symptoms of weakness, fatigue, anorexia, nausea, vomiting, abdominal pain (especially RUQ abdominal pain), jaundice, dark urine, generalized pruritus, and bleeding diathesis, especially in combination with fever and rash, should be reported immediately *[see Warnings and Precautions (5)]*.

17.2 Gastrointestinal Effects

Inform patients that nausea, diarrhea, vomiting, and constipation are 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)]*.

17.3 Visual Effects

Inform patients that visual changes such as perceived flashes of light, blurry vision, light sensitivity, and floaters are commonly reported adverse events. These events began most commonly during the first two weeks of treatment. Advise patients to report flashes or floaters to their physicians *[see Adverse Reactions (6)]*.

17.4 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, advise patients to exercise caution when driving or operating machinery due to the risk of developing a vision disorder, dizziness, or fatigue while taking XALKORI *[see Adverse Reactions (6)]*.

17.5 Concomitant Medications

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)]*.

17.6 Instructions for Taking XALKORI

Advise patients 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. Take XALKORI with or without food. Swallow XALKORI capsules whole.

Advise patients to keep XALKORI in the original container. Do not crush, dissolve, or open capsules.

Inform patients to avoid grapefruit or grapefruit juice while taking XALKORI.

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. Advise patients not to take two doses at the same time to make up for a missed dose.

17.7 Pregnancy and Nursing

Inform patients of childbearing potential to use adequate contraceptive methods during therapy and for at least 90 days after completing therapy. Advise patients to inform their doctor if they or their partners are pregnant or think they may be pregnant. Also advise patients not to breastfeed while taking XALKORI.

Manufactured by:

Pfizer manufacturing, Germany

License Holder:

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