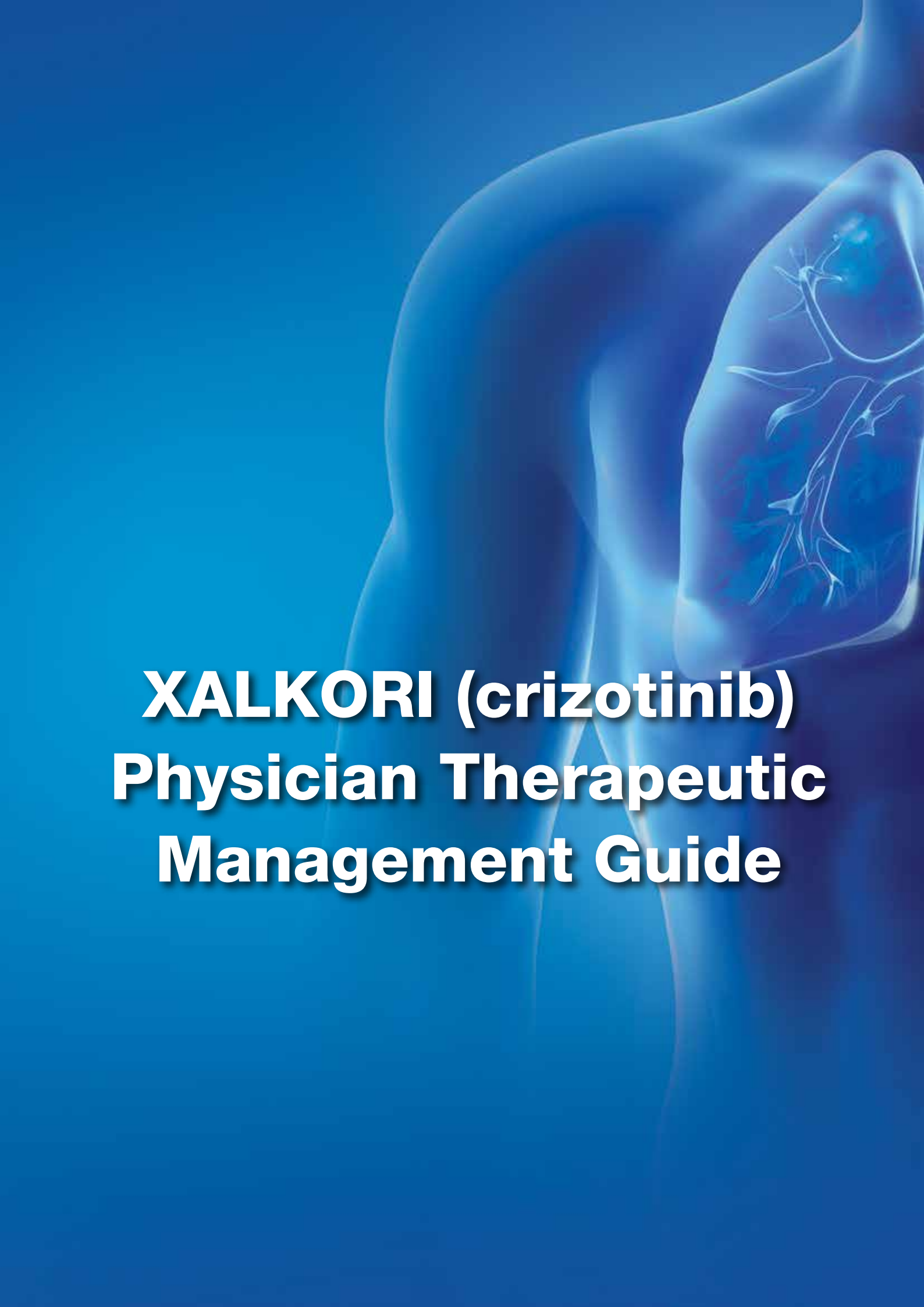


XALKORI (crizotinib) Physician Therapeutic Management Guide

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions

XALKORI® (crizotinib)
Therapeutic Management Guide

Physicians prescribing XALKORI should:

- Review this Therapeutic Management Guide and the full Product Information for XALKORI.
- Review the Patient booklet and Patient Alert Card and explain their role and use to patients who will receive XALKORI. The patient should be provided with the Patient booklet and Patient Alert Card with each prescription.

Crizotinib is indicated for the treatment of anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).

Reference: 1. XALKORI Summary of Product Characteristics. October 2015

PF-02341066-14 04
Date of preparation: October 2015

ALK-positive NSCLC status should be established prior to initiation of XALKORI therapy. An accurate and validated ALK assay is necessary for the selection of patients for treatment with XALKORI.

THE STANDARD DOSE SCHEDULE OF XALKORI® IS 250 MG TAKEN ORALLY TWICE DAILY CONTINUOUSLY

AM

*

PM

*

Standard dose: 500 mg/day1

*Capsule not shown in actual size.

ALK = anaplastic lymphoma kinase; NSCLC = non-small cell lung cancer

Reference: 1. XALKORI Summary of Product Characteristics. October2015

Adverse reactions reported with XALKORI

Safety evaluation of XALKORI is based on more than 1200 patients with ALK-positive metastatic NSCLC who received XALKORI as monotherapy at a starting oral dose of 250 mg twice daily continuously.

ALK-positive metastatic NSCLC-Study 1

The data in Table 3 are derived from 343 patients with ALK-positive metastatic NSCLC enrolled in a randomized, multicenter, active-controlled, open-label trial (Study 1). 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.

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=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 decreased appetite (27%), 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%).

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

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

ALK-positive metastatic NSCLC- Study 2

The safety analysis population in Study 2 included 934 patients with ALK-positive metastatic NSCLC who received XALKORI in a clinical trial. Dosing interruptions and reductions due to treatment-related adverse events occurred in 23% and 12% of patients, respectively. The rate of treatment-related adverse events resulting in permanent discontinuation was 5%. The most common adverse reactions (≥25%) included vision disorder (55%), nausea (51%), vomiting (46%), diarrhea (46%), edema (39%), constipation (38%), and fatigue (26%).

Reference: 1. XALKORI Summary of Product Characteristics. MMMM 2015

Adverse reactions reported with XALKORI

- 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.

- The most common adverse reactions (≥25%) of XALKORI are vision disorder, nausea, diarrhea, vomiting, constipation, edema, elevated transaminases, and fatigue.

Reference: 1. XALKORI Summary of Product Characteristics. October 2015

Management of adverse reactions with XALKORI
Hepatotoxicity

- Drug-induced hepatotoxicity with fatal outcome has occurred in less than 0.5% of patients with ALK-positive advanced NSCLC (N=1669), treated with XALKORI across clinical studies.[1]
- Concurrent elevations in ALT and/or AST≥ 3 x ULN and total bilirubin ≥2 x ULN without significant elevations of alkaline phosphatase (≤2 × ULN) have been observed in less than 1% patients in clinical trials.
- Increases to Grade 3 or 4 ALT or AST elevations were observed in 11% and 6% of patients, respectively.
- In PROFILE 1014, increases to Grade 3 or 4 ALT or AST elevations were observed in 15% and 8% of patients receiving crizotinib versus 2% and 1% of patients receiving chemotherapy. In PROFILE 1007, increases to Grade 3 or 4 ALT or AST elevations were observed in 18% and 9% of patients receiving crizotinib and 5% and <1% of patients receiving chemotherapy.
- Transaminase elevations generally occurred within the first 2 months of treatment. Grade 3 and 4 transaminase elevations were generally reversible upon dosing interruption. Across studies with crizotinib in patients with ALK-positive NSCLC (N=1669), dose reductions associated with transaminase elevations occurred in 4% of patients, and 1% of patients required permanent discontinuation from treatment.
- XALKORI should not be used in patients with severe hepatic impairment.

Transaminases (ALT, AST) and total bilirubin should be monitored once a week during the first 2 months of treatment, then once a month and as clinically indicated, with more frequent repeat testing for Grades 3 ,2 or 4 elevation.[1]

Patients should be monitored for hepatotoxicity. Treatment with XALKORI should be used with caution in patients with mild and moderate hepatic impairment.
XALKORI should not be used in patients with severe hepatic impairment.

It is important to counsel patients about the risk of hepatotoxicity and inform them of what symptoms and signs to be aware of and actions to take.

ALT = alanine aminotransferase; AST = aspartate aminotransferase.
Reference: 1. XALKORI Summary of Product Characteristics. MMMM 2015

Management of adverse reactions with XALKORI

DOSE MODIFICATION ON DETECTION OF TRANSAMINASE ELEVATIONS[1]	
Grade 3 or 4 ALT or AST elevation with Grade ≤1 total bilirubin	• Withhold until recovery to Grade ≤1 or baseline, then resume at 250 mg once daily and escalate to 200 mg twice daily if clinically tolerated*
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 haemolysis)	• Permanently discontinue

* XALKORI must be permanently discontinued in case of further Grade ≥3 recurrence.

Interstitial lung disease/pneumonitis

• Severe, life-threatening, and/or fatal interstitial lung disease (ILD)/pneumonitis can occur in patients treated with XALKORI. Across studies in patients with ALK-positive advanced NSCLC (N=1669), 3% of patients treated with crizotinib had any grade all-causality ILD, including 1% of patients with Grade 3 or 4, and <1% of patients with fatal cases. According to independent review committee (IRC) assessment, 20 (1.2%) patients had ILD/pneumonitis, including 10 (<1%) patients with fatal cases. These cases generally occurred within 3 months after the initiation of treatment. Other potential causes of ILD/pneumonitis should be excluded.

• Patients should be monitored for any pulmonary symptoms indicative of ILD/pneumonitis. XALKORI treatment should be withheld if ILD/pneumonitis is suspected. Drug-induced ILD/pneumonitis should be considered in the differential diagnosis of patients with ILD-like conditions such as: pneumonitis, radiation pneumonitis, hypersensitivity pneumonitis, interstitial pneumonitis, pulmonary fibrosis, acute respiratory distress syndrome (ARDS), alveolitis, lung infiltration, pneumonia, pulmonary oedema, chronic obstructive pulmonary disease, pleural effusion, aspiration pneumonia, bronchitis, obliterative bronchiolitis, and bronchiectasis.

• XALKORI treatment should be permanently discontinued in patients diagnosed with treatment-related ILD/pneumonitis.

DOSE MODIFICATION ON DETECTION OF PNEUMONITIS[1]	
Any Grade interstitial lung disease / pneumonitis*	• Withhold if interstitial lung disease / pneumonitis is suspected, and permanently discontinue if treatment-related ILD / pneumonitis is diagnosed

It is important to counsel patients about the risk of interstitial lung disease/pneumonitis and inform them of what symptoms and signs to be aware of and actions to take.

Reference: 1. XALKORI Summary of Product Characteristics. MMMM 2015.

Management of adverse reactions with XALKORI

QTc prolongation

- QTc prolongation has been observed, which may lead to an increased risk for ventricular tachyarrhythmias (e.g., Torsade de Pointes) or sudden death.
- Across studies in patients with ALK-positive advanced NSCLC, QTcF ≥500 msec was recorded in 2.1% of 1560 patients and a maximum increase from baseline in QTcF ≥60 msec was observed in 5.0% of 1520 patients. Grade 3 or 4 all-causality Electrocardiogram QT prolonged was reported in 1.5% out of 1669 patients.

DOSE MODIFICATION ON DETECTION OF QTC PROLONGATION[1]	
Grade 3	• Withhold until recovery to Grade ≤1, check and if necessary correct electrolytes, then resume at 200 mg twice daily*
Grade 4	• Permanently discontinue

* XALKORI must be permanently discontinued in case of further Grade >3 recurrence.

The benefits and potential risks of XALKORI should be considered before beginning therapy in patients with pre-existing bradycardia, who have a history of or predisposition for QTc prolongation, who are taking antiarrhythmics or other medicinal products that are known to prolong QT interval and in patients with relevant pre-existing cardiac disease, and/or electrolyte disturbances.

XALKORI should be administered with caution in these patients and periodic monitoring of electrocardiograms (ECG), electrolytes and renal function is required.

ECG and electrolytes (e.g., calcium, magnesium, potassium) should be obtained as close as possible prior to the first dose of XALKORI and periodic monitoring with ECGs and electrolytes is recommended, especially at the beginning of treatment in case of vomiting, diarrhoea, dehydration or impaired renal function. Correct electrolytes as necessary.

If QTc increases by greater than or equal to 60 msec from baseline but QTc is < 500 msec, crizotinib should be withheld and cardiologist advice should be sought. If QTc increases to greater than or equal to 500 msec, cardiologist advice must be immediately sought [1].

It is important to counsel patients about the risk of prolonged QTc and inform them of what symptoms to be aware of and actions to take.

QTc = corrected QT interval.

Reference: 1. XALKORI Summary of Product Characteristics. MMMM 2015

Management of adverse reactions with XALKORI

Bradycardia

Across studies with crizotinib in patients with ALK-positive advanced NSCLC (N=1669), all-causality bradycardia was experienced by 12% of patients treated with crizotinib. Symptomatic bradycardia (e.g., syncope, dizziness, hypotension) can occur in patients receiving XALKORI.

Avoid using crizotinib in combination with other bradycardic agents (e.g., beta-blockers, non-dihydropyridine calcium channel blockers such as verapamil and diltiazem, clonidine, digoxin) to the extent possible, due to the increased risk of symptomatic bradycardia.
Monitor heart rate and blood pressure regularly.
Dose modification is not required in cases of asymptomatic bradycardia. For management of patients who develop symptomatic bradycardia, see below.
It is important to counsel patients about the risk of bradycardia and inform them of what symptoms and signs to be aware of and actions to take.

DOSE MODIFICATION ON DETECTION OF BRADYCARDIA[1]	
Grade 2, 3 Bradycardia* Symptomatic, may be severe and medically significant, medical intervention indicated	• Withhold until recovery to Grade ≤ 1 or to heart rate 60 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 Grade ≤ 1 or to heart rate 60 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 Grade ≤ 1 or to heart rate 60 or above
Grade 4 Bradycardia* ‡ 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 Grade ≤ 1 or to heart rate 60 or above, with frequent monitoring

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

Reference: 1. XALKORI Summary of Product Characteristics. MMMM 2015

Management of adverse reactions with XALKORI

Visual effects

- Across studies in patients with ALK-positive advanced NSCLC (N=1669), all-causality vision disorder, most commonly visual impairment, photopsia, vision blurred, and vitreous floaters, was experienced by 62% of patients treated with crizotinib. Ninety-five percent of these patients had events that were mild in severity. The onset of vision disorders generally was within the first week of crizotinib administration.

- A total of 0.4% of patients had temporary treatment discontinuation and 0.1% of patients had a dose reduction associated with vision disorder. There were no permanent treatment discontinuations associated with vision disorder for any of the 1669 patients treated with crizotinib.

Ophthalmological evaluation (e.g., visual acuity, fundoscopy, and slit lamp examinations) should be considered if visual effects persist or worsen. [1]

Patients who experience visual effects should be advised to take special care when driving and using machines.[1]

Counsel patients about the risk of vision disorders and inform them of what symptoms to be aware of and the actions to take.

Reference: 1. XALKORI Summary of Product Characteristics. MMMM 2015

Management of adverse reactions with XALKORI

Gastrointestinal effects

- Nausea, diarrhoea, vomiting, and constipation were the most commonly reported all-causality gastrointestinal events. Median times to onset for nausea and vomiting were 4 days. Most of these events were mild to moderate in severity, and declined in frequency after 3 to 4 weeks. Supportive care should include the use of antiemetic medicinal products.

- Diarrhoea and constipation were primarily mild to moderate in severity. Supportive care for diarrhoea and constipation should include the use of standard antidiarrheal and laxative medications, respectively.

Reference: 1. XALKORI Summary of Product Characteristics. MMMM 2015

Management of adverse reactions with XALKORI

Nervous system effects

- Across studies in patients with ALK-positive advanced NSCLC (N=1669), all-causality neuropathy was experienced by 25% of patients treated with crizotinib. Dysgeusia was very commonly reported in these studies, and was primarily Grade 1 in severity.

Reference: 1. XALKORI Summary of Product Characteristics. MMMM 2015

Management of adverse reactions with XALKORI

Renal Cyst

- Across studies in patients with ALK-positive advanced NSCLC (N=1669), all-causality complex renal cysts were experienced by 3% of patients treated with crizotinib.

- Local cystic invasion beyond the kidney was observed in some patients.

Periodic monitoring with imaging and urinalysis should be considered in patients who develop renal cysts.

Reference: 1. XALKORI Summary of Product Characteristics. MMMM 2015

Management of adverse reactions with XALKORI

Neutropenia and leukopenia

• Across studies in patients with ALK-positive advanced NSCLC (N=1669) Grade 3 or 4 neutropenia was observed in 12% of patients treated with crizotinib. Median time to onset of any grade neutropenia was 87 days. Neutropenia was associated with dose reduction or permanent treatment discontinuation for 4% and <1% of patients, respectively. Less than 0.5% of patients experienced febrile neutropenia in clinical studies with crizotinib.

• Across studies in patients with ALK-positive advanced NSCLC (N=1669), Grade 3 or Grade 4 leukopenia was observed in 3% of patients. Median time to onset of any grade leukopenia was 85 days. Leukopenia was associated with a dose reduction for <0.5% of patients, and no patients permanently discontinued crizotinib treatment associated with leukopenia.

• In clinical studies of crizotinib in patients with ALK-positive advanced NSCLC, shifts to Grade 3 or 4 decreases in leukocytes and neutrophils were observed at frequencies of 4% and 14%, respectively.

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

DOSE MODIFICATION ON DETECTION OF HAEMATOLOGIC TOXICITIES†[1]	
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 *

† Except lymphopenia (unless associated with clinical events, e.g., opportunistic infections).
* In case of recurrence, withhold until recovery to Grade ≤2, then resume at 250 mg taken orally once daily Permanently discontinue in case of further Grade 4 recurrence

Reference: 1. XALKORI Summary of Product Characteristics. MMMM 2015

Administration of XALKORI in patients with severe renal impairment

XALKORI plasma concentrations may be increased in patients with severe renal impairment (CLcr <30 mL/min) not requiring peritoneal dialysis or hemodialysis.[1]

XALKORI starting dose should be adjusted to 250 mg taken orally once daily in patients with severe renal impairment not requiring peritoneal dialysis or hemodialysis.
The dose may be increased to 200 mg twice daily based on individual safety and tolerability after at least 4 weeks of treatment[1]

Coadministration of XALKORI with other medications

Agents that may increase XALKORI plasma concentrations

- Coadministration of XALKORI with strong CYP3A inhibitors may increase XALKORI plasma concentrations[1]

Avoid concomitant use of strong CYP3A inhibitors including certain protease inhibitors (e.g. atazanavir, indinavir, nelfinavir, ritonavir, and saquinavir), certain azole antifungals (e.g., itraconazole, ketoconazole, and voriconazole) and certain macrolides (e.g., clarithromycin, telithromycin, and troleandomycin).[1]

Avoid consumption of grapefruit or grapefruit juice.[1]

Agents that may decrease XALKORI plasma concentrations

- Coadministration of XALKORI with strong CYP3A inducers may decrease XALKORI plasma concentrations[1]

Avoid concurrent use of strong CYP3A inducers, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, and St. John's wort.[1]

CYP3A = cytochrome P4503A.

Reference: 1. XALKORI Summary of Product Characteristics. MMMM 2015

Coadministration of XALKORI with other medications

Agents whose plasma concentrations may be altered by XALKORI

- **XALKORI is a moderate inhibitor of CYP3A.[1]**

Coadministration of XALKORI with CYP3A substrates with narrow therapeutic indices, including but not limited to alfentanil, cisapride, cyclosporine, ergot derivatives, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus should be avoided.

- **XALKORI is an inhibitor of CYP2B6*[1]**

XALKORI may have the potential to increase plasma concentrations of coadministered drugs that are metabolized by CYP2B6 (e.g., bupropion, efavirenz).

- **XALKORI may induce PXR- and CAR-regulated enzymes (e.g., CYP3A4, CYP2B6 CYP2C8, CYP2C9, UGT1A1)*[1]**

Exercise caution in administering XALKORI in combination with medicinal products that are predominantly metabolised by these enzymes – the effectiveness of concomitant administration of oral contraceptives may be reduced.

- **XALKORI may be a P-gp inhibitor at therapeutic concentrations.*[1]**

Exercise caution in administering XALKORI as it may have the potential to increase plasma concentrations of coadministered medicinal products that are substrates of P-gp (e.g., digoxin, dabigatran, colchicine, pravastatin).

- **XALKORI is a weak inhibitor of UGT1A1 and UGT2B7.*[1]**

XALKORI may have the potential to increase plasma concentrations of coadministered drugs that are metabolized predominantly by UGT1A1 (e.g., raltegravir, irinotecan) or UGT2B7 (e.g., morphine, naloxone).

- **XALKORI is an inhibitor of OCT1 and OCT2*[1]**

XALKORI may have the potential to increase plasma concentrations of coadministered drugs that are substrates of OCT1 or OCT2 (e.g., metformin, procainamide).

*In vitro data.

CYP3A = cytochrome P4503A; P-gp = permeability glycoprotein; PXR = pregnane X receptor; CAR = constitutive androstane receptor.

Reference: 1. XALKORI Summary of Product Characteristics. MMMM 2015.

Dose modification guidance

- Dosing interruption and/or dose reduction may be required based on individual safety and tolerability

- Please refer to the Summary of Product Characteristics for dose adjustment guidelines for haematologic and non-haematologic toxicities[1]

RECOMMENDED POSOLOGY[1]

	AM	PM
250 mg BID	 *	 *

Standard dose: 500 mg/day[1]

	AM	PM
200 mg BID	 *	 *

If dose reduction is necessary: 400 mg/day[1]

250 mg QD  *

If further dose reduction is necessary: 250 mg/day[1]

Dose reduction may be required based on individual safety and tolerability[1]

*Capsule not shown in actual size.

BID = twice daily; QD = once daily

Reference: 1. XALKORI Summary of Product Characteristics. MMMM 2015.

- Please refer to the Summary of Product Characteristics for further guidance on dosing interruptions and dose reductions.

In 1669 patients treated with crizotinib with ALK-positive advanced NSCLC across clinical studies, the most frequent adverse reactions (≥3%, all-causality frequency) associated with dosing interruptions were neutropenia, (11 %), elevated transaminases (7%), vomiting, (5%), and nausea (4%). The most frequent adverse reactions (≥3%, all-causality frequency) associated with dose reductions were elevated transaminases, (4%), and neutropenia. (4%).

Please report any adverse events through the following channels

1. The National Pharmacovigilance & Drug Safety Centre (NPC)
   Fax: +966-11-205-7662
   Call NPC at +966-11-2038222, Ext:2317-2356-2353-2354-2334-2340.
   Toll free phone: 8002490000
   E-mail: npc.drug@sfda.gov.sa
   Website: www.sfda.gov.sa/npc

Or

2. The Pharmacovigilance Department in Pfizer:
   Email: SAU.AEReporting@Pfizer.com
   Tel.: 012 22 93520

XALKORI
Prescribing information

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----------

Crizotinib is indicated for the treatment of anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).

----------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----------

Hepatotoxicity: Drug-induced hepatotoxicity with fatal outcome has 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. (5.1)

- 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. (5.2)
- 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, consider periodic monitoring with electrocardiograms and electrolytes. (5.3)
- ALK Testing: Detection of ALK-positive NSCLC is necessary for selection of patients for treatment with Crizotinib because these are the only patients for whom benefit has been shown. 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.
- 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.

Revised: 02/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

Crizotinib is indicated for the treatment of anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).

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 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

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 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 bilirubin in 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 is necessary for selection of patients for treatment with Crizotinib because these are the only patients for whom benefit has been shown. 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.

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, apprise the patient 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 (≥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 persistent 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 occurred in 12 (5%) patients treated with XALKORI. All of these cases were Grade 1 or 2 in severity.

Complex renal cysts occurred 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 occurred 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)]*. 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 136 patients in Study A, 19 (14%) were 65 years or older. Of the 119 patients in Study B, 16 (13%) 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 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)]*.

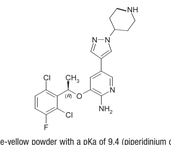
10. OVERDOSAGE

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 4.6. Steady state systemic exposure (C_{ss} 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$_{\tau,ss}$ 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 suggest 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$_{\infty}$ 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$_{\infty}$ 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$_{\tau}$ 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[1]

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 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

Do not store above 30°C.

17. PATIENT COUNSELING INFORMATION

See 17.6 for FDA-Approved Patient Labeling.

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.

17.8 FDA-Approved Patient Labeling

LAB-0440-5.0
Revised February 2012

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 for me to know about XALKORI?

XALKORI may cause serious side effects, such as:

Liver problems – XALKORI may cause life-threatening and/or fatal liver injury. 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
- you have itching

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

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.
  - o 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.
  - o Talk to your doctor about the birth control methods that may be right for you.
  - o 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?

Do not store above 30°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.

Bulk Manufacturer: Pfizer Manufacturing Deutschland GmbH (Betriebsstätte Freiburg), Freiburg, Germany.

Packaged and Released by: Pfizer Pharmaceuticals LLC,KM 1.9 Road 689,Vega Baja, Puerto Rico 00693

MAH: Pfizer Inc.

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

LAB-0441-3.0
Revised: February 2012

THIS IS A MEDICAMENT

- Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the Pharmacist who sold the medicament.
- The doctor and the Pharmacist are experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.

Keep all medicaments out of reach of children

Council of Arab Health Ministers
Union of Arabic Pharmacists

Distributed by

Pfizer Labs
Division of Pfizer Inc, NY, NY 10017

معلومات للمريض

زالكوري® (كريزوتينيب) كبسولات

يرجى قراءة نشرة معلومات المريض هذه بأكملها قبل البدء في تناول عقار زالكوري وفي كل مرة تحصل فيها على كمية جديدة من الدواء. قد تكون هناك معلومات جديدة. إن هذا لا يحل من التحدث مع الطبيب الخاص بك حول حالتك أو علاجك.

ما هي المعلومات الأكثر أهمية لمعرفتها بخصوص عقار زالكوري التي يتوجب علي معرفتها؟

قد يسبب عقار زالكوري اثارا جانبية خطيرة مثل:

مشاكل في الكبد: قد يتسبب عقار **زالكوري** في إصابة الكبد بشكل قد يهدد الحياة و / أو قد يكون مميتاً. ينبغي على الطبيب الخاص بك إجراء اختبار الدم بالدم بصفة شهرية لفحص الكبد أثناء تناولك لعقار زالكوري. أخبر الطبيب الخاص بك فورًا إذا كنت تعاني من أيٍ مما يلي:

- تغير لون جلدك أو بياض عينيك إلى اللون الأصفر
- الشعور بالتعب
- تغير لون البول إلى لون غامق أو بني (لون الشاي)
- غثيان أو قيء
- انخفاض الشهية
- ألم في الجانب الأيمن من معدتك
- قابلية للنزيف أو التكلم بسهولة عن المعتاد
- حكة

تورم الرئة (التهاب رئوي) - قد يتسبب عقار **زالكوري** في تورم (التهاب) الرئة بشكل قد يهدد الحياة و / أو قد يكون مميتاً أثناء العلاج. قد تكون الأعراض مشابهة لتلك الأعراض الناجمة عن سرطان الرئة. أخبر الطبيب الخاص بك فورًا إذا كان لديك أيٍ أعراض جديدة أو مصاحبة ومنها:

- صعوبة في التنفس أو هشيق في التنفس.
- سعال مع أو بدون مخاط (بلغم).
- حمى.

انظر "ما هي الآثار الجانبية المحتملة لعقار زالكوري" لمزيد من المعلومات حول الآثار الجانبية.

ما هو عقار زالكوري؟

عقار زالكوري هو وصفة دوائية لمستخدم لعلاج المرضى المصابين بسرطان الخلايا غير الصغيرة الرئوي (NSCLC) المتقدم أو المنتشر إلى أجزاء أخرى من الجسم والناتج عن خلل في جين يسمى كيناز الليمفوما ألك المنشيطة (ALK).

من غير المعروف ما إذا كان استخدام عقار زالكوري في الأطفال آمنًا وفعالاً.

ما الذي يتوجب علي إخبار طبيبي به قبل تناول عقار زالكوري؟

قبل تناول عقار زالكوري، أخبر الطبيب الخاص بك إذا:

- كان لديك مشاكل في القلب بما في ذلك حالة تسمى بمتلازمة إطالة فترة QT.
- كان لديك مشاكل في الكبد أو الكلى.
- كان لديك أية ظروف طبية أخرى.
- كنت حاملاً أو تخططين لذلك فقد يضر عقار زالكوري بجنينك.
  - o يجب على النساء ممن لديهن القدرة على الحمل والرجال الذين يتناولون عقار زالكوري استخدام وسائل منع الحمل خلال فترة العلاج ولمدة ٣ أشهر بعد وقف عقار زالكوري.
  - o يُرجى التحدث مع الطبيب الخاص بك حول طرق منع الحمل المناسبة لك.
  - o إذا أصبحت/ أصبحت زوجتك حاملاً، أخبري/ أخبر الطبيب الخاص بك/ بزوجتك على الفور.
- كنت ترضعين أو تخططين لذلك فمن غير المعروف ما إذا كان عقار زالكوري يمر إلى لبن الأم. يجب أن تقرري أنت وطبيبك ما إذا كنت سترضعين عقار زالكوري أم ترضعين. لا يجب عليك القيام بكلا هما معاً.

أخبر الطبيب الخاص بك عن الأدوية التي تتناولها، بما في ذلك الأدوية التي يتم الحصول عليها بوصفة طبية أو بدون، والفيتامينات والمكملات العشبية.

خاصة في حالة تناول:

- عشبة سانت جون (هوفاريفون)
- أدوية لعلاج:
  - الاكتئاب (مضادات الاكتئاب)
  - العدوى الفطرية (مضادات الفطريات)
  - العدوى الجرثومية (المضادات الحيوية)
  - الدرن
  - مرض الإيدز
  - امراض القلب
  - نوبات الصرع

يجب عليك معرفة الأدوية التي تتناولها. يُرجى الاحتفاظ بقائمة بها لعرضها على الطبيب أو الصيدلي الخاص بك عند الحصول على دواء جديد.

كيف يمكنني تناول عقار زالكوري؟

- تناول عقار زالكوري تمامًا كما أخبرك الطبيب الخاص بك.
- ابلع كبسولات عقار زالكوري كاملةً.
- لا تقم بسحق أو تذويب أو فتح الكبسولات.
- يمكن تناول عقار زالكوري مع أو بدون طعام.
- لا تقم بتغيير الجرعة أو توقف عقار زالكوري ما لم يخبرك طبيبك بذلك.
- إذا نسيت تناول جرعة، تناولها بمجرد تذكرها، أما إذا كان قد حان موعد الجرعة التالية (في غضون ٦ ساعات) فتناول فقط الجرعة التالية في وقتها المحدد.
- لا تتناول أكثر من جرعة واحدة من عقار زالكوري في نفس الوقت.
- اتصل بالطبيب الخاص بك فورًا في حالة تناول عقار زالكوري بكمية أكثر مما يجب.
- سيقوم الطبيب الخاص بك بإجراء فحوصات للدم والطب أثناء تناولك لعقار زالكوري.

ما الذي يجب علي تجنبه أثناء تناول عقار زالكوري؟

- يجب عدم تناول عصير الجريب فروت أو فاكهة الجريب فروت أثناء العلاج بعقار زالكوري. لأنه قد يؤدي إلى ارتفاع مستويات عقار زالكوري بالدم إلى مستويات ضارة.
- يمكن أن يُسبب عقار زالكوري تغيرات في الرؤية، الدوخة، والتعب. إذا كان لديك هذه الأعراض، فُرجى توخي الحذر عند قيادة السيارة، واستخدام الآلات أو القيام بأي عمل يحتاج منك إلى التركيز.

ما هي الآثار الجانبية المحتملة لعقار زالكوري؟

قد يسبب عقار زالكوري اثارا جانبية خطيرة:

- **انظر "ما هي المعلومات الأكثر أهمية الخاصة بعقار زالكوري التي يتوجب علي معرفتها؟"**
- تغيرات في ضربات القلب (تُسمى إطالة فترة QT): نبضات سريعة جدًا أو غير طبيعية. قد يقوم الطبيب الخاص بك بفحص قلبك أثناء العلاج بعقار زالكوري. أخبر الطبيب الخاص بك فورًا إذا كنت ضربات القلب لديك غير طبيعية، أو تشعر بدوار أو إغماء. قد تكون هذه الأعراض مرتبطة بإطالة فترة QT.

الآثار الجانبية الأكثر شيوعا لعقار زالكوري تتضمن:

- مشاكل في الرؤية
- تحدث هذه المشاكل عادة خلال الأسبوع الثاني من بدء العلاج بعقار زالكوري. أخبر طبيبك فورًا إذا كان لديك أيٌ تغيير في الرؤية، مثل:
  - ومضات ضوئية
  - عدم وضوح الرؤية
  - تضرر عينيك من الضوء
  - شوائب جديدة أو زائدة بسائل العين
- الغثيان
- الإسهال
- القيء
- تورم اليدين والقدمين
- الامساك

أخبر طبيبك إذا كان لديك أيٌ أثر جانبي يزعجك أو لا يزول. هذه ليست كل الآثار الجانبية المحتملة لعقار زالكوري. لمزيد من المعلومات، اسأل الطبيب أو الصيدلي الخاص بك.

اتصل بطبيبك للحصول على المشورة الطبية حول الآثار الجانبية ويمكنك الإبلاغ عن الآثار الجانبية إلى إدارة الغذاء والدواء الأمريكية (FDA) على الهاتف المجاني رقم 1-800-FDA-1088.

كيف أقوم بتخزين عقار زالكوري؟

يحفظ في درجة حرارة لا تزيد عن ٣٠ درجة مئوية.

- احفظ عقار زالكوري داخل العبوة الأصلية، وتأكد من اغلاقها بإحكام.
- لا تلمس أو تتعامل مع كبسولات عقار زالكوري المكسورة أو المسحوقة فقد تم صنع عقار زالكوري في كبسولات لمنع التلامس مع المادة الفعالة.

احفظ عقار زالكوري وجميع الأدوية بعيدًا عن متناول الأطفال.

معلومات عامة عن عقار زالكوري

توصف أحيانًا الأدوية لأغراض أخرى غير تلك المدرجة في نشرة معلومات المريض. لا تستخدم عقار زالكوري لأغراض غير التي تم وصفها لك. لا تعطه للآخرين حتى إذا كانوا يعانون من نفس الأعراض التي تعاني أنت منها فقد يضر بهم.

تُوفر هذه النشرة أهم المعلومات عن عقار زالكوري. إذا كنت ترغب في معرفة المزيد عن عقار زالكوري تحدث مع الطبيب الخاص بك. يمكنك أن تسأل الطبيب أو الصيدلي الخاص بك للحصول على مزيد من المعلومات حول عقار زالكوري.

لمزيد من المعلومات، قم بزيارة الموقع الإلكتروني www.XALKORI.com

ما هي مكونات عقار زالكوري؟

المادة الفعالة: كريزوتينيب

المكونات غير الفعالة: ثاني أكسيد السيليكون الغروي، السليلوز دقيق التبلور، فوسفات الكالسيوم ثنائي القاعدة اللامائي، جليكولات نشا الصوديوم، وستيارات المغنيسيوم

يحتوي غلاف الكبسولة الوردي الحمام على: جيلاتين، ثاني أكسيد التيتانيوم، وأكسيد الحديد الأحمر.

يحتوي غلاف الكبسولة الأبيض الحمام على: جيلاتين، ثاني أكسيد التيتانيوم.

يحتوي حبر الطباعة على: شلاك، بايلوكل البروبيلين ، محلول أمونيا قوي، هيدروكسيد البوتاسيوم، وأكسيد الحديد الأسود.

الشركة المصنعة:

Pfizer Manufacturing Deutschland GmbH (Betriebsstätte Freiburg), Freiburg, Germany.

الشركة المعبئة و المصرح:

Pfizer Pharmaceuticals LLC,KM 1.9 Road 689,Vega Baja, Puerto Rico 00693

ملك حق التفويض بالتسويق:

Pfizer Inc.

تم اعتماد معلومات المريض هذه من قبل إدارة الغذاء والدواء الأمريكية.

تاريخ مراجعة النشرة : شباط / فبراير ٢٠١٢

ان هذا الدواء

الدواء مستحضر طبي يؤثر على صحتك و استخدامه خلافًا للتعليمات يعرضك للخطر.
اتبع بدقة وصفة الطبيب و طريقة الاستعمال المنصوص عليها و تعليمات الصيدلاني الذي صرفها لك.
إن الطبيب و الصيدلاني هما الخبيرين بمنافع و مخاطر الأدوية.
لا تقطع مدة العلاج المحددة لك من تلقاء نفسك.
لا تكرر أبدا الوصفة الطبية من تلقاء نفسك و بدون استشارة الطبيب.

احتفظ بجميع الأدوية بعيداً عن متناول الأطفال

مجلس وزراء الصحة العرب
والاتحاد الصيدلاني العرب

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