

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XALKORI® safely and effectively. See full prescribing information for XALKORI.

XALKORI® (crizotinib) capsules, for oral use

Initial U.S. Approval: 2011

RECENT MAJOR CHANGES

Indications and Usage (1.2)	1/2021
Dosage and Administration (2.3, 2.4, 2.5, 2.6, 2.7, 2.8)	1/2021
Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.5, 5.6)	1/2021

INDICATIONS AND USAGE

XALKORI is a kinase inhibitor indicated for the treatment of

- patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK) or ROS1-positive as detected by an FDA-approved test. (1.1, 2.1)
- pediatric patients 1 year of age and older and young adults with relapsed or refractory, systemic anaplastic large cell lymphoma (ALCL) that is ALK-positive. (1.2, 2.3)
 - Limitations of Use: The safety and efficacy of XALKORI have not been established in older adults with relapsed or refractory, systemic ALK-positive ALCL.

DOSAGE AND ADMINISTRATION

- Metastatic NSCLC: The recommended dosage is 250 mg orally twice daily. (2.2)
- Systemic ALCL: The recommended dosage is 280 mg/m² orally twice daily based on body surface area. (2.3)
- See full prescribing information for dosage adjustments by indication for patients with moderate or severe hepatic impairment or severe renal impairment. (2.6, 2.7)

DOSAGE FORMS AND STRENGTHS

Capsules: 250 mg, 200 mg. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Hepatotoxicity: Fatal hepatotoxicity has occurred. Monitor with periodic liver testing. Temporarily suspend, dose reduce, or permanently discontinue XALKORI. (2.5, 5.1)
- Interstitial Lung Disease (ILD)/Pneumonitis: Permanently discontinue in patients with ILD/pneumonitis. (2.5, 5.2)

- QT Interval Prolongation: Monitor electrocardiograms and electrolytes in patients who have a history of or predisposition for QTc prolongation, or who are taking medications that prolong QT. Temporarily suspend, dose reduce, or permanently discontinue XALKORI. (2.5, 5.3)
- Bradycardia: XALKORI can cause bradycardia. Monitor heart rate and blood pressure regularly. Temporarily suspend, dose reduce, or permanently discontinue XALKORI. (2.5, 5.4)
- Severe Visual Loss: XALKORI can cause visual changes including severe visual loss. Discontinue XALKORI in patients with severe visual loss. Monitor and evaluate for ocular toxicity throughout treatment. (2.5, 5.5)
- Gastrointestinal Toxicity in Patients with ALCL: XALKORI can cause severe nausea, vomiting, diarrhea, and stomatitis. Provide standard antiemetic and antidiarrheal agents. Temporarily suspend, dose reduce, or permanently discontinue XALKORI. (2.4, 2.5, 5.6)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception. (5.7, 8.1, 8.3)

ADVERSE REACTIONS

The most common adverse reactions (≥25%) in patients with NSCLC are vision disorders, nausea, diarrhea, vomiting, edema, constipation, elevated transaminases, fatigue, decreased appetite, upper respiratory infection, dizziness, and neuropathy. (6.1)

The most common adverse reactions (≥35%) in patients with ALCL, excluding laboratory abnormalities, are diarrhea, vomiting, nausea, vision disorder, headache, musculoskeletal pain, stomatitis, fatigue, decreased appetite, pyrexia, abdominal pain, cough, and pruritus. Grade 3-4 laboratory abnormalities (≥15%) are neutropenia, lymphopenia, and thrombocytopenia. (6.1)

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

- Strong CYP3A Inhibitors: Avoid concomitant use. (2.8, 7.1)
- Strong CYP3A Inducers: Avoid concomitant use. (7.1)
- CYP3A Substrates: Avoid concomitant use with CYP3A substrates, where minimal concentration changes may lead to serious adverse reactions. (7.2)

USE IN SPECIFIC POPULATIONS

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 9/2021

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 ALK- or ROS1-Positive Metastatic Non-Small Cell Lung Cancer

XALKORI is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK) or ROS1-positive as detected by an FDA-approved test [*see Dosage and Administration (2.1)*].

1.2 Relapsed or Refractory, Systemic ALK-Positive Anaplastic Large Cell Lymphoma

XALKORI is indicated for the treatment of pediatric patients 1 year of age and older and young adults with relapsed or refractory, systemic anaplastic large cell lymphoma (ALCL) that is ALK-positive.

Limitations of Use: The safety and efficacy of XALKORI have not been established in older adults with relapsed or refractory, systemic ALK-positive ALCL.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for the treatment of metastatic NSCLC with XALKORI based on the presence of ALK or ROS1 positivity in tumor specimens [*see Clinical Studies (14.1, 14.2)*].

Information on FDA-approved tests for the detection of ALK and ROS1 rearrangements in NSCLC is available at <http://www.fda.gov/companiondiagnostics>.

2.2 Recommended Dosage for ALK- or ROS1-Positive Metastatic Non-Small Cell Lung Cancer

The recommended dosage of XALKORI for patients with NSCLC is 250 mg orally twice daily, with or without food, until disease progression or no longer tolerated by the patient.

Swallow capsules whole. If a dose of XALKORI is missed, make up that dose unless the next dose is due within 6 hours. If vomiting occurs after taking a dose of XALKORI, take the next dose at the regular time.

2.3 Recommended Dosage for Relapsed or Refractory, Systemic ALK-Positive Anaplastic Large Cell Lymphoma

The recommended dosage of XALKORI for patients with ALCL is 280 mg/m² orally twice daily until disease progression or unacceptable toxicity. The recommended dosage of XALKORI is based on body surface area (BSA) is provided in Table 1. If needed, attain the desired dose by combining different strengths of XALKORI capsules.

Assess pediatric patients for their ability to swallow intact capsules before prescribing XALKORI. Administer XALKORI to pediatric patients under adult supervision.

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

Table 1. Recommended XALKORI Dosage for Patients with ALCL

Body Surface Area *	Recommended XALKORI Dosage
0.60 – 0.80 m ²	200 mg orally twice daily
0.81 – 1.16 m ²	250 mg orally twice daily
1.17 – 1.51 m ²	400 mg orally twice daily
1.52 – 1.69 m ²	450 mg orally twice daily
1.70 m ² or greater	500 mg orally twice daily

* The recommended dosage for patients with a BSA less than 0.60 m² has not been established.

2.4 Concomitant Treatments for Patients with ALCL

Provide standard antiemetic and antidiarrheal agents for gastrointestinal toxicities. Antiemetics are recommended prior to and during treatment with XALKORI to prevent nausea and vomiting.

Consider intravenous or oral hydration for patients at risk of dehydration, and replace electrolytes as clinically indicated [see *Warnings and Precautions (5.6)*].

2.5 Dosage Modifications for Adverse Reactions

Recommended Dosage Reductions

ALK- or ROS1-positive metastatic NSCLC

The recommended dose reductions for adverse reactions in patients with metastatic NSCLC are:

- First dose reduction: XALKORI 200 mg taken orally twice daily
- Second dose reduction: XALKORI 250 mg taken orally once daily
- Permanently discontinue if unable to tolerate XALKORI 250 mg taken orally once daily.

Systemic ALK-positive ALCL

The recommended dose reductions for adverse reactions in patients with ALCL are provided in Table 2.

Table 2. Recommended Dose Reductions for XALKORI in Patients with ALCL

Body Surface Area	First Dose Reduction	Second Dose Reduction
	Dose	Dose
0.60 – 0.80 m ²	250 mg Once daily	Permanently discontinue
0.81 – 1.16 m ²	200 mg Twice daily	250 mg Once daily*
1.17 – 1.69 m ²	250 mg Twice daily	200 mg Twice daily*
1.70 m ² or greater	400 mg Twice daily	250 mg Twice daily*

* Permanently discontinue in patients who are unable to tolerate XALKORI after 2 dose reductions.

Recommended Dosage Modifications for Patients with NSCLC

Recommended dosage modifications for hematologic and non-hematologic adverse reactions for patients with NSCLC are provided in Tables 3 and 4.

Table 3. Patients with NSCLC: XALKORI Dosage Modification – Hematologic Toxicities^a

Severity of Adverse Reaction ^b	XALKORI Dosage Modification
Grade 3	Withhold until recovery to Grade 2 or less, then resume at the same dosage.
Grade 4	Withhold until recovery to Grade 2 or less, then resume at next lower dosage.

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

^b Grade based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

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.

Table 4. Patients with NSCLC: XALKORI Dosage Modification – Non-Hematologic Toxicities

Severity of Adverse Reaction ^a	XALKORI Dosage Modification
Hepatotoxicity [see Warnings and Precautions (5.1)]	
Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 5 times upper limit of normal (ULN) with total bilirubin less than or equal to 1.5 times ULN	Withhold until recovery to baseline or less than or equal to 3 times ULN, then resume at next lower dosage.
ALT or AST greater than 3 times ULN with concurrent total bilirubin greater than 1.5 times ULN (in the absence of cholestasis or hemolysis)	Permanently discontinue.
Interstitial Lung Disease (Pneumonitis) [see Warnings and Precautions (5.2)]	
Any grade drug-related interstitial lung disease/pneumonitis	Permanently discontinue.
QT Interval Prolongation [see Warnings and Precautions (5.3)]	
QT corrected for heart rate (QTc) greater than 500 ms on at least 2 separate electrocardiograms (ECGs)	Withhold until recovery to baseline or to a QTc less than 481 ms, then resume at next lower dosage.
QTc greater than 500 ms or greater than or equal to 60 ms change from baseline with Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	Permanently discontinue.
Bradycardia [see Warnings and Precautions (5.4)]	
Bradycardia ^b (symptomatic, may be severe and medically significant, medical intervention indicated)	Withhold until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. Evaluate concomitant medications known to cause bradycardia, as well as antihypertensive medications. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at previous dose upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, resume at reduced dose upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above.
Bradycardia ^{b,c} (life-threatening consequences, urgent intervention indicated)	Permanently discontinue if no contributing concomitant medication is identified. If contributing concomitant medication is identified and

Severity of Adverse Reaction ^a	XALKORI Dosage Modification
	discontinued, or its dose is adjusted, resume at 250 mg once daily upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring.
Severe Visual Loss [see Warnings and Precautions (5.5)]	
Visual Loss (Grade 4 Ocular Disorder)	Discontinue during evaluation of severe visual loss.

^a Grade based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

^b Heart rate less than 60 beats per minute (bpm).

^c Permanently discontinue for recurrence.

Recommended Dosage Modifications for Patients with ALCL

Recommended dosage modifications for hematologic and non-hematologic adverse reactions for patients with ALCL are provided in Tables 5 and 6.

Table 5. Patients with ALCL: XALKORI Dosage Modification for Hematologic Adverse Reactions

Severity of Adverse Reaction	XALKORI Dosage Modification
Absolute Neutrophil Count (ANC)	
Less than $0.5 \times 10^9/L$	<p>First occurrence: Withhold until recovery to ANC greater than $1.0 \times 10^9/L$, then resume at the next lower dosage.</p> <p>Second occurrence:</p> <ul style="list-style-type: none"> Permanently discontinue for recurrence complicated by febrile neutropenia or infection. For uncomplicated Grade 4 neutropenia, either permanently discontinue, or withhold until recovery to ANC greater than $1.0 \times 10^9/L$, then resume at the next lower dosage.^a
Platelet Count	
25 to $50 \times 10^9/L$ with concurrent bleeding	Withhold until recovery to platelet count greater than $50 \times 10^9/L$ and bleeding resolves, then resume at the same dosage.
Less than $25 \times 10^9/L$	Withhold until recovery to platelet count greater than $50 \times 10^9/L$, then resume at the next lower dosage. Permanently discontinue for recurrence.
Anemia	
Hemoglobin less than 8 g/dL	Withhold until recovery to hemoglobin 8 g/dL or more, then resume at the same dosage.
Life-threatening anemia; urgent intervention indicated.	Withhold until recovery to hemoglobin 8 g/dL or more, then resume at the next lower dosage. Permanently discontinue for recurrence.

^a Permanently discontinue in patients who are unable to tolerate XALKORI after 2 dose reductions, unless otherwise indicated in Table 2.

Monitor complete blood counts including differential weekly for the first month of therapy and then at least monthly, with more frequent monitoring if Grade 3 or 4 abnormalities, fever, or infection occur.

Table 6. Patients with ALCL: XALKORI Dosage Modification for Non-Hematologic Adverse Reactions

Severity of Adverse Reaction ^a	XALKORI Dosage Modification
Hepatotoxicity [see Warnings and Precautions (5.1)]	
Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 5 times upper limit of normal (ULN) with total bilirubin less than or equal to 1.5 times ULN	Withhold until recovery to baseline or less than or equal to 3 times ULN, then resume at next lower dosage.
ALT or AST greater than 3 times ULN with concurrent total bilirubin greater than 1.5 times ULN (in the absence of cholestasis or hemolysis)	Permanently discontinue.
Interstitial Lung Disease (Pneumonitis) [see Warnings and Precautions (5.2)]	
Any grade drug-related interstitial lung disease/pneumonitis	Permanently discontinue.
QT Interval Prolongation [see Warnings and Precautions (5.3)]	
QT corrected for heart rate (QTc) greater than 500 ms on at least 2 separate electrocardiograms (ECGs)	Withhold until recovery to baseline or to a QTc less than 481 ms, then resume at next lower dosage.
QTc greater than 500 ms or greater than or equal to 60 ms change from baseline with Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	Permanently discontinue.
Bradycardia [see Warnings and Precautions (5.4)]	
Bradycardia ^b (symptomatic, may be severe and medically significant, medical intervention indicated)	Withhold until recovery to a resting heart rate according to the patient's age (based on the 2.5 th percentile per age-specific norms) as follows: <ul style="list-style-type: none"> • 1 to <2 years: 91 bpm or above • 2 to 3 years: 82 bpm or above • 4 to 5 years: 72 bpm or above • 6 to 8 years: 64 bpm or above • >8 years: 60 bpm or above
Bradycardia ^{b,c} (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 the second dose reduction level in Table 2 ^c upon recovery to asymptomatic bradycardia or to the heart rate criteria listed for management of symptomatic or severe, medically significant bradycardia, with frequent monitoring.
Ocular Toxicity, including Visual Loss [see Warnings and Precautions (5.5)]	
Visual Symptoms, Grade 1 (mild symptoms) or Grade 2 (moderate symptoms affecting ability to perform age-appropriate activities of daily living)	Monitor symptoms and report any symptoms to an eye specialist. Consider dose reduction for Grade 2 visual disorders.
Visual Loss (Grade 3 or 4 Ocular Disorder, marked decrease in vision)	Withhold pending evaluation of severe visual loss. Permanently discontinue XALKORI for Grade 3 or 4 ocular disorders, if no other cause found on evaluation.

Severity of Adverse Reaction ^a	XALKORI Dosage Modification
Gastrointestinal Toxicity [<i>see Warnings and Precautions (5.6)</i>]	
Nausea (Grade 3: inadequate oral intake for more than 3 days, medical intervention required)	Grade 3 (despite maximum medical therapy): Withhold until resolved, and then resume at the next lower dose level. ^d
Vomiting (Grade 3: more than 6 episodes in 24 hours for more than 3 days, medical intervention required, i.e. tube feeding or hospitalization; Grade 4: life-threatening consequences, urgent intervention indicated)	Grade 3 or 4 (despite maximum medical therapy): Withhold until resolved, and then resume at the next lower dose level. ^d
Diarrhea (Grade 3: increase of 7 or more stools per day over baseline; incontinence; hospitalization indicated; Grade 4: life-threatening consequences, urgent intervention indicated)	Grade 3 or 4 (despite maximum medical therapy): Withhold until resolved, and then resume at the next lower dose level. ^d

^a Grade based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

^b Adult patients: Heart rate less than 60 beats per minute (bpm); Pediatric patients: Resting heart rate less than the 2.5th percentile per age-specific norms.

^c Permanently discontinue for recurrence.

^d Permanently discontinue in patients who are unable to tolerate XALKORI after 2 dose reductions, unless otherwise indicated in Table 2.

2.6 Dosage Modifications for Moderate and Severe Hepatic Impairment

ALK- or ROS1-positive metastatic NSCLC

The recommended dose of XALKORI in patients with moderate hepatic impairment [any aspartate aminotransferase (AST) and total bilirubin greater than 1.5 times the upper limit of normal (ULN) and less than or equal to 3 times ULN] is 200 mg orally twice daily.

The recommended dose of XALKORI in patients with severe hepatic impairment (any AST and total bilirubin greater than 3 times ULN) is 250 mg orally once daily [*see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)*].

Systemic ALK-positive ALCL

The recommended dose of XALKORI in patients with moderate hepatic impairment [any aspartate aminotransferase (AST) and total bilirubin greater than 1.5 times the upper limit of normal (ULN) and less than or equal to 3 times ULN] is the first dose reduction based on BSA as shown in Table 2 [*see Dosage and Administration (2.5), Use in Specific Populations (8.6), Clinical Pharmacology (12.3)*].

The recommended dose of XALKORI in patients with severe hepatic impairment (any AST and total bilirubin greater than 3 times ULN) is the second dose reduction based on BSA as shown in Table 2 [*see Dosage and Administration (2.5), Use in Specific Populations (8.6), Clinical Pharmacology (12.3)*].

2.7 Dosage Modification for Severe Renal Impairment

ALK- or ROS1-positive metastatic NSCLC

The recommended dosage of XALKORI in patients with severe renal impairment [creatinine clearance (CL_{cr}) less than 30 mL/min, calculated using the modified Cockcroft-Gault equation] not requiring dialysis is 250 mg orally once daily [*see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)*].

Systemic ALK-positive ALCL

The recommended dosage of XALKORI in patients with severe renal impairment (CL_{cr}) less than 30 mL/min, calculated using the modified Cockcroft-Gault equation for adult patients and the Schwartz equation for pediatric patients not requiring dialysis is the second dose reduction based on BSA as shown in Table 2 [see *Dosage and Administration (2.5)*, *Use in Specific Populations (8.7)*, *Clinical Pharmacology (12.3)*].

2.8 Dosage Modification for Concomitant Use of Strong CYP3A Inhibitors

ALK- or ROS1-positive metastatic NSCLC

Avoid concomitant use of strong CYP3A inhibitors. If concomitant use of strong CYP3A inhibitors is unavoidable, reduce the dose of XALKORI to 250 mg orally once daily [see *Drug Interactions (7.1)*]. After discontinuation of a strong CYP3A inhibitor, resume the XALKORI dose used prior to initiating the strong CYP3A inhibitor.

Systemic ALK-positive ALCL

Avoid concomitant use of strong CYP3A inhibitors. If concomitant use of strong CYP3A inhibitors is unavoidable, reduce the dose of XALKORI to the second dose reduction based on BSA as shown in Table 2 [see *Dosage and Administration (2.5)*, *Drug Interactions (7.1)*]. After discontinuation of a strong CYP3A inhibitor, resume the XALKORI dose used prior to initiating the strong CYP3A inhibitor.

3 DOSAGE FORMS AND STRENGTHS

Capsules:

- 250 mg: hard gelatin capsule, size 0, pink opaque cap and body, with “Pfizer” on the cap and “CRZ 250” on the body.
- 200 mg: hard gelatin capsule, size 1, white opaque body and pink opaque cap, with “Pfizer” on the cap and “CRZ 200” on the body.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity

Drug-induced hepatotoxicity with fatal outcome occurred in 0.1% of the 1719 patients treated with XALKORI for NSCLC across clinical trials [see *Adverse Reactions (6.1)*]. Concurrent elevations in ALT or AST ≥ 3 times the ULN and total bilirubin ≥ 2 times the ULN, with normal alkaline phosphatase, occurred in <1% of patients treated with XALKORI. Increased ALT or AST >5 times the ULN occurred in 11% and 6% of patients, respectively. One percent (1.0%) of patients required permanent discontinuation due to elevated transaminases. Increased transaminases generally occurred within the first 2 months of treatment.

In Study ADVL0912, of 121 patients ages 1 to ≤ 21 years treated with XALKORI for relapsed or refractory tumors including ALCL, 71% and 79% had increases of AST and ALT, respectively, with increased ALT or

AST >5 times the ULN in 6% each. Of the 26 patients with ALCL treated with XALKORI, 65% and 81% had increases of AST and ALT, respectively, with increases >5 times the ULN in 4% each.

Monitor liver function tests, including ALT, AST, and total bilirubin, every 2 weeks during the first 2 months of treatment, then once a month, and as clinically indicated, with more frequent repeat testing for increased liver transaminases, alkaline phosphatase, or total bilirubin in patients who develop increased transaminases. Withhold, reduce dose, or permanently discontinue XALKORI for hepatotoxicity as recommended [*see Dosage and Administration (2.5)*].

5.2 Interstitial Lung Disease/Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD)/pneumonitis can occur in patients treated with XALKORI. Across clinical trials in patients with NSCLC (n=1719), 2.9% of XALKORI-treated patients had ILD of any grade, 1% had Grade 3 or 4 ILD, and 0.5% had fatal ILD [*see Adverse Reactions (6.1)*]. Interstitial lung disease generally occurred within 3 months after the initiation of XALKORI.

In Study ADVL0912, among 121 patients ages 1 to \leq 21 years with relapsed or refractory tumors, including ALCL, ILD occurred in 0.8% of patients.

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis. Exclude other potential causes of ILD/pneumonitis, and permanently discontinue XALKORI in patients diagnosed with drug-related ILD/pneumonitis [*see Dosage and Administration (2.5)*].

5.3 QT Interval Prolongation

QTc prolongation can occur in patients treated with XALKORI. Across clinical trials in patients with NSCLC, 2.1% of 1616 patients had QTcF (corrected QT for heart rate by the Fridericia method) greater than or equal to 500 ms and 5% of 1582 patients had an increase from baseline QTcF greater than or equal to 60 ms by automated machine-read evaluation of ECGs.

In Study ADVL0912, QTc prolongation was reported as an adverse reaction in 4.1% of patients, including 8% of patients with ALCL.

Avoid use of XALKORI in patients with congenital long QT syndrome. Monitor 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. Withhold, reduce dose, or permanently discontinue XALKORI for QT/QTc interval prolongation as recommended [*see Dosage and Administration (2.5), Clinical Pharmacology (12.2)*].

5.4 Bradycardia

Symptomatic bradycardia can occur in patients receiving XALKORI. Across clinical trials in patients with NSCLC, bradycardia occurred in 13% of 1719 patients treated with XALKORI. Grade 3 syncope occurred in 2.4% of XALKORI-treated patients and in 0.6% of the chemotherapy-treated patients [*see Adverse Reactions (6.1)*].

In Study ADVL0912, among 121 patients ages 1 to \leq 21 years treated with XALKORI, bradycardia was reported in 14%, including Grade 3 bradycardia in 0.8% of patients. Of the 26 patients with ALCL treated with XALKORI, bradycardia (all Grade 1) was reported in 19%.

Avoid using XALKORI in combination with other medications known to cause bradycardia (e.g., beta-blockers, non-dihydropyridine calcium channel blockers, clonidine, and digoxin) to the extent possible. Monitor heart rate and blood pressure regularly. If bradycardia occurs, re-evaluate for the use of concomitant medications known to cause bradycardia. Withhold, reduce dose, or permanently discontinue XALKORI for bradycardia as recommended [*see Dosage and Administration (2.5)*].

5.5 Severe Visual Loss

Across all clinical trials in patients with NSCLC, the incidence of Grade 4 visual field defect with visual loss was 0.2% of 1719 patients [*see Adverse Reactions (6.1)*]. Optic atrophy and optic nerve disorder have been reported as potential causes of visual loss.

In Study ADVL0912, visual disorders occurred in 46% of 121 patients with XALKORI, including 65% of 26 patients with ALCL. Of the 56 patients who experienced visual disorders, one patient experienced Grade 3 optic nerve disorder. The most common visual symptoms were blurred vision and visual impairment.

For patients with ALCL, obtain baseline ophthalmologic examination prior to starting XALKORI. Follow-up ophthalmologic examination including retinal examination is recommended within 1 month of starting XALKORI, every 3 months thereafter, and upon any new visual symptoms. Assessment of visual symptoms is recommended monthly during treatment. Report any visual symptoms to an eye specialist. Withhold XALKORI pending evaluation for any Grade 3 or 4 ocular disorders, and permanently discontinue XALKORI for Grade 3 or 4 ocular disorders unless another cause is identified [*see Dosage and Administration (2.5)*].

Discontinue XALKORI in any patient with new onset of severe visual loss (best corrected vision less than 20/200 in one or both eyes). Perform an ophthalmological evaluation consisting of best corrected visual acuity, retinal photographs, visual fields, optical coherence tomography (OCT), and other evaluations as appropriate for new onset of visual loss and for other visual symptoms as clinically warranted [*see Dosage and Administration (2.5), Adverse Reactions (6.1)*].

There is insufficient information to characterize the risks of resumption of XALKORI in patients who develop visual symptoms or visual loss. A decision to resume XALKORI should consider the potential benefits versus risks to the patient.

5.6 Gastrointestinal Toxicity in Patients with ALCL

XALKORI can cause severe gastrointestinal toxicities in patients with ALCL [*see Adverse Reactions (6.1)*]. In patients with ALCL (n=26), gastrointestinal toxicity occurred in 100% of patients; Grade 3 gastrointestinal toxicity occurred in 27% of patients and included diarrhea, nausea, vomiting, and stomatitis.

Provide standard antiemetic and antidiarrheal agents for gastrointestinal toxicities in patients with ALCL. Antiemetics are recommended prior to and during treatment with XALKORI to prevent nausea and vomiting. If patients develop Grade 3 nausea lasting 3 days or Grade 3 or 4 diarrhea or vomiting despite maximum medical therapy, withhold XALKORI until resolved, and then resume at the next lower dose level. Consider supportive care such as hydration, electrolyte supplementation, and nutritional support as clinically indicated [*see Dosage and Administration (2.5)*].

5.7 Embryo-Fetal Toxicity

Based on its mechanism of action, XALKORI can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, oral administration of crizotinib in pregnant rats during organogenesis at exposures similar to those observed with the maximum recommended human dose resulted in embryotoxicity and fetotoxicity. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with XALKORI and for at least 45 days following the final dose. Advise males with female partners of reproductive potential to use condoms during treatment with XALKORI and for at least 90 days after the final dose [see *Use in Specific Populations (8.1, 8.3), Nonclinical Toxicology (13.1)*].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hepatotoxicity [see *Warnings and Precautions (5.1)*]
- Interstitial Lung Disease/Pneumonitis [see *Warnings and Precautions (5.2)*]
- QT Interval Prolongation [see *Warnings and Precautions (5.3)*]
- Bradycardia [see *Warnings and Precautions (5.4)*]
- Severe Visual Loss [see *Warnings and Precautions (5.5)*]
- Gastrointestinal Toxicity in Patients with ALCL [see *Warnings and Precautions (5.6)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data in the Warnings and Precautions reflect exposure to XALKORI in 1719 patients with NSCLC who received XALKORI 250 mg twice daily enrolled on Studies 1 (including an additional 109 patients who crossed over from the control arm), 2, 3, a single-arm trial (n=1063) of ALK-positive NSCLC, and an additional ALK-positive NSCLC expansion cohort of a dose finding study (n=154). The data also reflect exposure to XALKORI in 121 patients ages 1 to ≤ 21 years with relapsed or refractory tumors, including 26 patients with systemic ALCL, in a single-arm trial (Study ADVL0912).

ALK- or ROS1-Positive Metastatic NSCLC

The data described below is based primarily on 343 patients with ALK-positive metastatic NSCLC who received XALKORI 250 mg orally twice daily from 2 open-label, randomized, active-controlled trials (Studies 1 and 2). The safety of XALKORI was also evaluated in 50 patients with ROS1-positive metastatic NSCLC from a single-arm study (Study 3).

The most common adverse reactions ($\geq 25\%$) of XALKORI in patients with NSCLC are vision disorders, nausea, diarrhea, vomiting, edema, constipation, elevated transaminases, fatigue, decreased appetite, upper respiratory infection, dizziness, and neuropathy.

Previously Untreated ALK-Positive Metastatic NSCLC - Study 1 (PROFILE 1014)

The data in Table 7 are derived from 340 patients with ALK-positive metastatic NSCLC who had not received previous systemic treatment for advanced disease who received treatment in a randomized, multicenter, open-label, active-controlled trial (Study 1). Patients in the XALKORI arm (n=171) received XALKORI

250 mg orally twice daily until documented disease progression, intolerance to therapy, or the investigator determined that the patient was no longer experiencing clinical benefit. A total of 169 patients in the chemotherapy arm received pemetrexed 500 mg/m² with cisplatin 75 mg/m² (n=91) or carboplatin at a dose calculated to produce an AUC of 5 or 6 mg×min/mL (n=78). Chemotherapy was given by intravenous infusion every 3 weeks for up to 6 cycles, in the absence of dose-limiting chemotherapy-related toxicities. After 6 cycles, patients remained on study with no additional anticancer treatment, and tumor assessments continued until documented disease progression.

The median duration of study treatment was 10.9 months for patients in the XALKORI arm and 4.1 months for patients in the chemotherapy arm. Median duration of treatment was 5.2 months for patients who received XALKORI after cross over from chemotherapy. Across the 340 patients who were treated in Study 1, the median age was 53 years; 16% of patients were older than 65 years. A total of 62% of patients were female and 46% were Asian.

Serious adverse events were reported in 34% of patients treated with XALKORI. The most frequent serious adverse events reported in patients treated with XALKORI were dyspnea (4.1%) and pulmonary embolism (2.9%). Fatal adverse events in XALKORI-treated patients occurred in 2.3% patients, consisting of septic shock, acute respiratory failure, and diabetic ketoacidosis.

Dose reductions due to adverse reactions were required in 6% of XALKORI-treated patients. The most frequent adverse reactions that led to dose reduction in these patients were nausea (1.8%) and elevated transaminases (1.8%).

Permanent discontinuation of XALKORI treatment for adverse reactions was 8%. The most frequent adverse reactions that led to permanent discontinuation in XALKORI-treated patients were elevated transaminases (1.2%), hepatotoxicity (1.2%), and ILD (1.2%).

Tables 7 and 8 summarize common adverse reactions and laboratory abnormalities in XALKORI-treated patients.

Table 7. Adverse Reactions Reported at a Higher Incidence ($\geq 5\%$ Higher for All Grades or $\geq 2\%$ Higher for Grades 3-4) with XALKORI than Chemotherapy in Study 1[†]

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

[†] Adverse reactions were graded using NCI CTCAE version 4.0.

Includes cases reported within the clustered terms:

^a Bradycardia (Bradycardia, Sinus bradycardia).

^b Vision Disorder (Diplopia, Photophobia, Photopsia, Reduced visual acuity, Blurred vision, Vitreous floaters, Visual impairment).

^c Abdominal pain (Abdominal discomfort, Abdominal pain, Lower abdominal pain, Upper abdominal pain, Abdominal tenderness).

^d Esophagitis (Esophagitis, Esophageal ulcer).

^e Edema (Edema, Peripheral edema, Face edema, Generalized edema, Local swelling, Periorbital edema).

^f Upper respiratory infection (Nasopharyngitis, Pharyngitis, Rhinitis, Upper respiratory tract infection).

^g Dizziness (Balance disorder, Dizziness, Postural dizziness, Presyncope).

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

Clinically relevant adverse reactions in <1% of patients who received XALKORI included photosensitivity (0.3%).

Table 8. Laboratory Abnormalities with Grades 3-4 Occurring in ≥4% of XALKORI-Treated Patients in Study 1

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

Additional laboratory test abnormality in patients treated with XALKORI was an increase in creatinine (Any Grade: 99%; Grade 3: 2%; Grade 4: 0%) compared to the chemotherapy arm (Any Grade: 92%; Grade 3: 0%; Grade 4: 1%).

Previously Treated ALK-Positive Metastatic NSCLC - Study 2 (PROFILE 1007)

The data in Table 9 are derived from 343 patients with ALK-positive metastatic NSCLC enrolled in a randomized, multicenter, active-controlled, open-label trial (Study 2). Patients in the XALKORI arm (n=172) received XALKORI 250 mg orally twice daily until documented disease progression, intolerance to therapy, or the investigator determined that the patient was no longer experiencing clinical benefit. A total of 171 patients in the chemotherapy arm received pemetrexed 500 mg/m² (n=99) or docetaxel 75 mg/m² (n=72) by intravenous infusion every 3 weeks until documented disease progression, intolerance to therapy, or the investigator determined that the patient was no longer experiencing clinical benefit. Patients in the chemotherapy arm received pemetrexed unless they had received pemetrexed as part of first-line or maintenance treatment.

The median duration of study treatment was 7.1 months for patients who received XALKORI and 2.8 months for patients who received chemotherapy. Across the 347 patients who were randomized to study treatment (343 received at least 1 dose of study treatment), the median age was 50 years; 14% of patients were older than 65 years. A total of 56% of patients were female and 45% of patients were Asian.

Serious adverse reactions were reported in 37% of patients treated with XALKORI and 23% of patients in the chemotherapy arm. The most frequent serious adverse reactions reported in patients treated with XALKORI were pneumonia (4.1%), pulmonary embolism (3.5%), dyspnea (2.3%), and ILD (2.9%). Fatal adverse reactions in XALKORI-treated patients in Study 2 occurred in 5% of patients, consisting of: acute respiratory distress syndrome, arrhythmia, dyspnea, pneumonia, pneumonitis, pulmonary embolism, ILD, respiratory failure, and sepsis.

Dose reductions due to adverse reactions were required in 16% of XALKORI-treated patients. The most frequent adverse reactions that led to dose reduction in the patients treated with XALKORI were increased ALT (8%) including some patients with concurrent increased AST, QTc prolongation (2.9%), and neutropenia (2.3%).

XALKORI was discontinued for adverse reactions in 15% of patients. The most frequent adverse reactions that led to discontinuation of XALKORI were ILD (1.7%), increased ALT and AST (1.2%), dyspnea (1.2%), and pulmonary embolism (1.2%).

Tables 9 and 10 summarize common adverse reactions and laboratory abnormalities in XALKORI-treated patients.

Table 9. Adverse Reactions Reported at a Higher Incidence ($\geq 5\%$ Higher for All Grades or $\geq 2\%$ Higher for Grades 3-4) with XALKORI than Chemotherapy in Study 2[†]

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

[†] Adverse reactions were graded using NCI CTCAE version 4.0.

Includes cases reported within the clustered terms:

^a Dizziness (Balance disorder, Dizziness, Postural dizziness).

^b Vision Disorder (Diplopia, Photophobia, Photopsia, Blurred vision, Reduced visual acuity, 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, Peripheral edema, 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, paresthesia, peripheral sensory neuropathy, polyneuropathy, burning sensation in skin), rash (9%), ILD (4%; acute respiratory distress syndrome, ILD, pneumonitis), renal cyst (4%), esophagitis (2%), hepatic failure (1%), and decreased blood testosterone (1%; hypogonadism).

Clinically relevant adverse reactions in <1% of patients who received XALKORI included photosensitivity (0.4%).

Table 10. Laboratory Abnormalities with Grades 3-4 Occurring in ≥4% of XALKORI-Treated Patients in Study 2

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

Additional laboratory test abnormality in patients treated with XALKORI was an increase in creatinine (Any Grade: 96%; Grade 3: 1%; Grade 4: 0%) compared to the chemotherapy arm (Any Grade: 72%; Grade 3: 0%; Grade 4: 0%).

ROS1-Positive Metastatic NSCLC - Study 3 (PROFILE 1001)

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

Description of Selected Adverse Reactions in Patients with Metastatic NSCLC

Vision disorders: Vision disorders, most commonly visual impairment, photopsia, blurred vision, or vitreous floaters, occurred in 63% of 1719 patients. The majority (95%) of these patients had Grade 1 visual adverse reactions. There were 0.8% of patients with Grade 3 and 0.2% of patients with Grade 4 visual impairment. Based on the Visual Symptom Assessment Questionnaire (VSAQ-ALK), patients treated with XALKORI in Studies 1 and 2 reported a higher incidence of visual disturbances compared to patients treated with chemotherapy. The onset of vision disorder generally was within the first week of drug administration. The majority of patients on the XALKORI arms in Studies 1 and 2 (>50%) reported visual disturbances which occurred at a frequency of 4-7 days each week, lasted up to 1 minute, and had mild or no impact (scores 0 to 3 out of a maximum score of 10) on daily activities as captured in the VSAQ-ALK questionnaire.

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

Renal cysts: Renal cysts were experienced by 3.0% of 1719 patients. The majority of renal cysts in XALKORI-treated patients were complex. Local cystic invasion beyond the kidney occurred, in some cases with imaging characteristics suggestive of abscess formation. However, across clinical trials no renal abscesses were confirmed by microbiology tests.

Renal toxicity: The estimated glomerular filtration rate (eGFR) decreased from a baseline median of 96.42 mL/min/1.73 m² (n=1681) to a median of 80.23 mL/min/1.73 m² at 2 weeks (n=1499) in patients with ALK-positive advanced NSCLC who received XALKORI in clinical trials. No clinically relevant changes occurred in median eGFR from 12 to 104 weeks of treatment. Median eGFR slightly increased (83.02 mL/min/1.73 m²) 4 weeks after the last dose of XALKORI. Overall, 76% of patients had a decrease in

eGFR to <90 mL/min/1.73 m², 38% had a decrease to eGFR to <60 mL/min/1.73 m², and 3.6% had a decrease to eGFR to <30 mL/min/1.73 m².

Relapsed or Refractory, Systemic ALK-Positive ALCL - Study ADVL0912

The safety of XALKORI was evaluated in Study ADVL0912 [see *Clinical Studies 14.2*], which included 26 patients with relapsed or refractory, systemic ALCL after at least one systemic therapy. Eligible patients were 1 to ≤21 years of age and were required to have an absolute neutrophil count ≥1000/mm³ (750/mm³ if bone marrow was involved), platelet count ≥75,000/mm³ (25,000/mm³ if bone marrow was involved), creatinine clearance ≥70ml/min/1.73m², and QTc ≤480 msec. The study excluded patients with ALT >2.5 times upper limit of normal (ULN), bilirubin ≤1.5 times ULN, and central nervous system tumors.

Patients with ALCL received XALKORI 165 mg/m² or 280 mg/m² orally twice daily until disease progression or unacceptable toxicity. The median duration of exposure was 5.4 months (range 1.8, 82.3 months), with 46% of patients treated for at least 6 months and 35% of patients treated for at least 12 months.

Serious adverse reactions occurred in 35% of patients treated with XALKORI. The most frequent serious adverse reactions were neutropenia (12%) and hypotension (8%).

Dose interruptions and dose reductions occurred in 77% and 19% of patients, respectively. XALKORI was discontinued for an adverse reaction in 8% of patients.

The most common adverse reactions (≥35%), excluding laboratory abnormalities, were diarrhea, vomiting, nausea, vision disorder, headache, musculoskeletal pain, stomatitis, fatigue, decreased appetite, pyrexia, abdominal pain, cough, and pruritis.

The most common Grade 3 or 4 laboratory abnormalities (≥15%) included neutropenia, lymphopenia, and thrombocytopenia. Grade 4 laboratory abnormalities (≥15%) included neutropenia (62%), lymphopenia (35%), and thrombocytopenia (19%).

Selected adverse reactions are summarized in Table 11.

Table 11. Adverse Reactions in ≥20% of Patients with Systemic ALCL in Study ADVL0912

Adverse Reaction	XALKORI N=26	
	All Grades (%)	Grade 3-4 (%)
Blood and Lymphatic System Disorders^a		
Neutropenia ^b	100	77
Lymphopenia ^c	58	38
Anemia	54	3.8
Thrombocytopenia ^d	38	19
Gastrointestinal Disorders		
Diarrhea	92	12
Vomiting	92	3.8
Nausea	77	3.8
Abdominal Pain	50	0
Stomatitis ^c	46	8
Constipation	31	0

Adverse Reaction	XALKORI N=26	
	All Grades (%)	Grade 3-4 (%)
Renal Disorders^a		
Blood creatinine increased	100	0
Investigations^a		
ALT increased	81	3.8
AST increased	65	3.8
Hypocalcemia	62	3.8
Hypoalbuminemia	54	0
Hyperglycemia	46	0
Hypomagnesemia	46	0
Hypoglycemia	35	0
Hypokalemia	31	3.8
Hypermagnesemia	27	0
Hyperkalemia	23	0
Nervous System Disorders		
Headache	58	3.8
Dysgeusia	23	0
Dizziness	23	0
Eye Disorders		
Vision disorders ^f	65	0
Musculoskeletal Disorders		
Musculoskeletal pain ^g	58	12
General Disorders		
Fatigue	46	0
Pyrexia	38	0
Edema ^h	27	0
Chills	23	0
Metabolism and Nutrition Disorders		
Decreased appetite	42	0
Skin and Subcutaneous Disorders		
Pruritus	35	0
Rash ⁱ	23	0
Infections		
Upper respiratory tract infection ^j	31	0
Respiratory Disorders		
Cough	35	0
Rhinitis allergic	23	0
Vascular Disorders		
Hypertension	31	0

Adverse reactions were graded using NCI CTCAE version 4.0.

^a Derived from laboratory values collected in Cycle 1 and adverse reaction data.

^b Includes neutrophil count decreased.

^c Includes lymphocyte count decreased.

^d Includes platelet count decreased.

^e Includes oral pain, oropharyngeal pain, stomatitis.

^f Includes blurred vision, visual impairment, photophobia, photopsia, reduced visual acuity, vitreous floaters, cyanopsia, heterophoria, visual field defect.

^g Includes arthralgia, back pain, myalgia, non-cardiac chest pain, pain in extremity.

^h Includes peripheral edema, face edema, periorbital edema, localized edema.

ⁱ Includes rash maculopapular, rash pustular.

^j Includes upper respiratory tract infection, pharyngitis, rhinitis, sinusitis.

Clinically relevant adverse reactions in <20% of patients treated with XALKORI included:

- **Cardiac disorders:** Bradycardia (19%), electrocardiogram QT prolonged (8%)
- **Vascular Disorders:** Hypotension (19%)
- **Investigations:** Alkaline phosphatase increase (19%), hypernatremia (19%), GGT increase (8%), hyponatremia (12%), hyperuricemia (12%), hypophosphatemia (12%)
- **Nervous System Disorders:** Peripheral neuropathy (12%)
- **Gastrointestinal disorders:** Esophagitis (8%)
- **Blood and lymphatic disorders:** Febrile neutropenia (3.8%)
- **Musculoskeletal disorders:** Muscular weakness (8%)
- **Renal Disorder:** Acute renal injury (8%)

6.2 Postmarketing Experience

The following additional adverse reaction has been identified during postapproval use of XALKORI. Because this reaction is reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

Investigations: Increased blood creatine phosphokinase

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on XALKORI

Strong or Moderate CYP3A Inhibitors

Concomitant use of crizotinib with strong CYP3A inhibitors increases crizotinib plasma concentrations [*see Clinical Pharmacology (12.3)*], which may increase the risk of adverse reactions of XALKORI. Avoid concomitant use of strong CYP3A inhibitors. If concomitant use of strong CYP3A inhibitors is unavoidable, reduce the XALKORI dosage [*see Dosage and Administration (2.8)*]. Avoid grapefruit or grapefruit juice which may also increase plasma concentrations of crizotinib. Use caution with concomitant use of moderate CYP3A inhibitors.

Strong CYP3A Inducers

Concomitant use of crizotinib with strong CYP3A inducers decreases crizotinib plasma concentrations [*see Clinical Pharmacology (12.3)*], which may decrease the efficacy of XALKORI. Avoid concomitant use of strong CYP3A inducers.

7.2 Effect of XALKORI on Other Drugs

CYP3A Substrates

Concomitant use of crizotinib increases plasma concentrations of CYP3A substrates [*see Clinical Pharmacology (12.3)*], which may increase the risk of adverse reactions of these substrates. Avoid concomitant use of XALKORI with CYP3A substrates where minimal concentration changes may lead to serious adverse reactions. If concomitant use of XALKORI is unavoidable, decrease the CYP3A substrate dosage in accordance with approved product labeling.

7.3 Drugs That Prolong the QT Interval

XALKORI can prolong the QT/QTc interval. Avoid concomitant use of XALKORI with drugs that prolong the QT interval [see *Warnings and Precautions* (5.3), *Clinical Pharmacology* (12.2)].

7.4 Drugs That Cause Bradycardia

XALKORI can cause bradycardia. Avoid concomitant use of XALKORI with drugs that cause bradycardia (e.g., beta-blockers, non-dihydropyridine calcium channel blockers, clonidine, and digoxin) [see *Warnings and Precautions* (5.4)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action, XALKORI can cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology* (12.1)]. There are no available data on the use of XALKORI during pregnancy. In animal reproduction studies, oral administration of crizotinib in pregnant rats during organogenesis at exposures similar to those expected with the maximum recommended human dose resulted in embryotoxicity and fetotoxicity (see *Data*). Advise pregnant women of the potential risk to fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

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

8.2 Lactation

Risk Summary

There is no information regarding the presence of crizotinib or its metabolites in human milk, or the effects on the breastfed child or on milk production. Because of the potential for adverse reactions in breastfed children, advise women not to breastfeed during treatment with XALKORI and for 45 days after the final dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating XALKORI [see *Use in Specific Population* (8.1)].

Contraception

XALKORI can cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*].

Females

Advise females of reproductive potential to use effective contraception during treatment with XALKORI and for at least 45 days after the final dose.

Males

Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with XALKORI and for at least 90 days after the final dose [*see Nonclinical Toxicology (13.1)*].

Infertility

Based on reproductive organ findings in animals, XALKORI may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible [*see Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

The safety and effectiveness of XALKORI have been established in pediatric patients 12 months of age and older with relapsed or refractory, systemic ALK-positive ALCL [*see Adverse Reactions (6.1), Clinical Studies (14.2)*]. The safety and effectiveness have not been established in pediatric patients younger than 12 months of age with ALCL or in any pediatric patients with NSCLC.

In a study that evaluated XALKORI in combination with chemotherapy in pediatric patients with newly diagnosed ALCL (Study ANHL12P1; NCT01979536), 13 of 66 (20%) patients had a Grade 2 or higher thromboembolic event, including pulmonary embolism in 6%. The safety and effectiveness of XALKORI in combination with chemotherapy have not been established in patients with newly diagnosed ALCL.

Juvenile Animal Toxicity Data

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

8.5 Geriatric Use

Of the total number of patients with ALK-positive metastatic NSCLC in clinical studies of XALKORI (n=1669), 16% were 65 years or older and 3.8% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Clinical studies of XALKORI in patients with ROS1-positive metastatic NSCLC did not include sufficient numbers of patients age 65 years and older to determine whether they respond differently from younger patients.

8.6 Hepatic Impairment

Crizotinib concentrations increased in patients with pre-existing moderate (any AST and total bilirubin greater than 1.5 times ULN and less than or equal to 3 times ULN) or severe (any AST and total bilirubin greater than 3 times ULN) hepatic impairment [see *Clinical Pharmacology (12.3)*]. Reduce XALKORI dosage in patients with moderate or severe hepatic impairment [see *Dosage and Administration (2.6)*]. No dose adjustment is recommended in patients with pre-existing mild hepatic impairment (AST > ULN and total bilirubin less than or equal to 1 times ULN or any AST and total bilirubin greater than 1 times ULN but less than or equal to 1.5 times ULN).

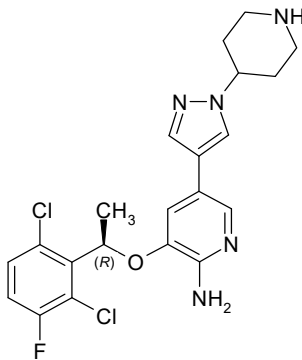
8.7 Renal Impairment

Increased exposure to crizotinib occurred in patients with pre-existing severe renal impairment (CL_{cr} less than 30 mL/min calculated using the modified Cockcroft-Gault equation for adult patients and the Schwartz equation for pediatric patients) not requiring dialysis, therefore reduce dosage of XALKORI in these patients [see *Dosage and Administration (2.7)*, *Clinical Pharmacology (12.3)*]. No dose adjustment is recommended in patients with mild to moderate renal impairment (CL_{cr} 30 to 89 mL/min).

11 DESCRIPTION

Crizotinib is a kinase inhibitor. The molecular formula for crizotinib is $C_{21}H_{22}Cl_2FN_5O$ and 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 (crizotinib) for oral administration is supplied as printed hard-shell capsules containing 250 mg or 200 mg of crizotinib together with colloidal silicon dioxide, microcrystalline cellulose, anhydrous dibasic calcium phosphate, sodium starch glycolate, magnesium stearate, and hard gelatin capsule shells as inactive ingredients.

The pink opaque capsule shell components contain gelatin, titanium dioxide, and red iron oxide. The white opaque capsule shell components contain gelatin and titanium dioxide. The printing ink contains shellac, propylene glycol, strong ammonia solution, potassium hydroxide, and black iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Crizotinib is an inhibitor of receptor tyrosine kinases including ALK, Hepatocyte Growth Factor Receptor (HGFR, c-Met), ROS1 (c-ros), and Recepteur d'Origine Nantais (RON). Translocations can affect the ALK gene resulting in the expression of oncogenic fusion proteins. The formation of ALK fusion proteins results in activation and dysregulation of the gene's expression and signaling which can contribute to increased cell proliferation and survival in tumors expressing these proteins. Crizotinib demonstrated concentration-dependent inhibition of ALK, ROS1, and c-Met phosphorylation in cell-based assays using tumor cell lines and demonstrated antitumor activity in mice bearing tumor xenografts that expressed echinoderm microtubule-associated protein-like 4 (EML4)- or nucleophosmin (NPM)-ALK fusion proteins or c-Met.

In vitro, crizotinib induced apoptosis and inhibited proliferation and ALK-mediated signaling in ALCL-derived cell lines (containing NPM-ALK) at clinically achievable exposures. In vivo data obtained in an ALCL-derived mouse model showed complete regression of the tumor at a dose of 100 mg/kg once daily.

12.2 Pharmacodynamics

Cardiac Electrophysiology

In an ECG substudy conducted in 52 patients with ALK-positive NSCLC, the maximum mean QTcF (corrected QT by the Fridericia method) change from baseline was 12.3 ms (2-sided 90% upper CI: 19.5 ms) following administration of XALKORI 250 mg orally twice daily. An exposure-QT analysis suggested a crizotinib plasma concentration-dependent increase in QTcF [*see Warnings and Precautions (5.3)*].

12.3 Pharmacokinetics

Following XALKORI 250 mg twice daily, steady-state was reached within 15 days and remained stable, with a median accumulation ratio of 4.8. Steady-state observed minimum concentration (C_{\min}) and AUC increased in a greater than dose-proportional manner over the dose range of 200 mg to 300 mg twice daily (0.8 to 1.2 times the approved recommended dosage).

Absorption

A single crizotinib dose was absorbed with median time to achieve peak concentration of 4 to 6 hours, and the mean absolute bioavailability of crizotinib was 43% (range: 32% to 66%).

Effect of Food

A high-fat meal reduced crizotinib AUC_{0-12h} and maximum observed plasma concentration (C_{\max}) by approximately 14%.

Distribution

The geometric mean volume of distribution (V_{ss}) of crizotinib was 1772 L following a single intravenous dose. Protein binding of crizotinib is 91% and is independent of drug concentration in vitro. Crizotinib is a substrate for P-glycoprotein (P-gp) in vitro. The blood-to-plasma concentration ratio is approximately 1.

Elimination

The mean apparent plasma terminal half-life of crizotinib was 42 hours following single doses of crizotinib in patients. The mean apparent clearance (CL/F) of crizotinib was lower at steady-state (60 L/h) after 250 mg twice daily than after a single 250 mg oral dose (100 L/h).

Metabolism

Crizotinib is predominantly metabolized by CYP3A.

Excretion

Following administration of a single oral 250 mg dose of radiolabeled crizotinib dose to healthy subjects, 63% (53% as unchanged) of the administered dose was recovered in feces and 22% (2.3% as unchanged) in urine.

Specific Populations

No clinically significant difference in crizotinib pharmacokinetics were observed based on age, sex, or ethnicity (Asian, non-Asian). For patients <18 years of age, body weight has a significant effect on the pharmacokinetics of crizotinib, with lower crizotinib exposures observed in patients with higher body weight.

Pediatric Patients

In pediatric patients with ALCL, crizotinib steady-state exposure increased proportionally with dose over the dose range of 165 mg/m² to 280 mg/m² orally twice daily. At a dosing regimen of 280 mg/m² (approximately 2 times the recommended adult dose), geometric mean (CV%) steady-state maximum plasma concentrations (C_{max}) of crizotinib was 621 (73%) ng/mL and AUC_{0-tau} was 6530 (34%) ng·hr/mL.

Patients with Hepatic Impairment

Steady-state mean crizotinib AUC and C_{max} decreased by 9% in patients with mild hepatic impairment (AST >ULN and total bilirubin ≤1 times ULN or any AST and total bilirubin >1 times ULN but ≤1.5 times ULN) compared to patients with normal hepatic function following XALKORI 250 mg orally twice daily.

Steady-state mean crizotinib AUC increased by 14% and C_{max} increased by 9% in patients with moderate hepatic impairment (any AST and total bilirubin >1.5 times ULN and ≤3 times ULN) following XALKORI 200 mg orally twice daily compared with patients with normal hepatic function following XALKORI 250 mg orally twice daily.

Mean crizotinib AUC decreased by 35% and C_{max} decreased by 27% in patients with severe hepatic impairment (any AST and total bilirubin >3 times ULN) following XALKORI 250 mg orally once daily compared with patients with normal hepatic function following XALKORI 250 mg orally twice daily [*see Dosage and Administration (2.6), Use in Specific Populations (8.6)*].

Patients with Renal Impairment

Mild or moderate renal impairment (CL_{cr} of 60-89 ml/min or 30-59 ml/min, respectively, calculated using the modified Cockcroft-Gault equation) has no clinically significant effect on the exposure of crizotinib. Following a single 250 mg dose, the mean AUC_{0-INF} of crizotinib increased by 79% and the mean C_{max} increased by 34% in patients with severe renal impairment (CL_{cr} <30 mL/min) who did not require dialysis compared to those with normal renal function (CL_{cr} ≥90 mL/min). Similar changes in AUC_{0-INF} and C_{max} were observed for the active metabolite of crizotinib [*see Dosage and Administration (2.7), Use in Specific Populations (8.7)*].

Drug Interaction Studies

Clinical Studies

Gastric Acid Reducing Agents: No clinically significant differences in crizotinib pharmacokinetics were observed when used concomitantly with esomeprazole, a proton pump inhibitor.

Strong CYP3A Inhibitors: Coadministration of a single 150 mg oral dose of crizotinib with ketoconazole, a strong CYP3A inhibitor, increased crizotinib AUC_{0-INF} by 216% and C_{max} by 44% compared to crizotinib alone. Coadministration of XALKORI 250 mg orally once daily with itraconazole, a strong CYP3A inhibitor, increased crizotinib steady-state AUC by 57% and C_{max} by 33% compared to crizotinib alone [*see Drug Interactions (7.1)*].

Strong CYP3A Inducers: Coadministration of XALKORI 250 mg orally twice daily with rifampin, a strong CYP3A inducer, decreased crizotinib steady-state AUC_{0-Tau} by 84% and C_{max} by 79%, compared to crizotinib alone [*see Drug Interactions (7.1)*].

CYP3A Substrates: Coadministration of XALKORI 250 mg orally twice daily for 28 days increased AUC_{0-INF} of oral midazolam (CYP3A substrate) 3.7-fold compared to midazolam alone [*see Drug Interactions (7.2)*].

In Vitro Studies

CYP Enzymes: Crizotinib inhibits CYP2B6 in vitro. Crizotinib does not inhibit CYP1A2, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. Crizotinib does not induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A.

UDP-glucuronosyltransferase (UGT): Crizotinib does not inhibit UGT1A1, UGT1A4, UGT1A6, UGT1A9 or UGT2B7.

Transporters: Crizotinib inhibits P-gp, organic cation transporter (OCT) 1, and OCT2. Crizotinib does not inhibit organic anion transporting polypeptides (OATP) B1, OATP1B3, organic anion transporter (OAT) 1, OAT3, or bile salt export pump transporter (BSEP).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with crizotinib have not been conducted.

Crizotinib was genotoxic in an in vitro micronucleus assay in Chinese Hamster Ovary cultures, in an in vitro human lymphocyte chromosome aberration assay, and in in vivo rat bone marrow micronucleus assays. Crizotinib was not mutagenic in vitro in the bacterial reverse mutation (Ames) assay.

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

14 CLINICAL STUDIES

14.1 ALK- or ROS1-Positive Metastatic Non-Small Cell Lung Cancer

Previously Untreated ALK-Positive Metastatic NSCLC - Study 1 (PROFILE 1014; NCT01154140)

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

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

The demographic characteristics of the overall study population were 62% female, median age of 53 years, baseline ECOG performance status 0 or 1 (95%), 51% White and 46% Asian, 4% current smokers, 32% past smokers, and 64% never smokers. The disease characteristics of the overall study population were metastatic disease in 98% of patients, 92% of patients' tumors were classified as adenocarcinoma histology, 27% of patients had brain metastases, and 7% received systemic chemotherapy as adjuvant or neoadjuvant therapy. At the time of the final analysis of overall survival, 84% of patients randomized to the chemotherapy arm subsequently received XALKORI.

Study 1 demonstrated a statistically significant improvement in PFS in patients treated with XALKORI. There was no statistically significant difference in OS between patients treated with XALKORI and patients treated with chemotherapy. Table 12 and Figure 1 summarize the efficacy results. Exploratory patient-reported symptom measures of baseline and post-treatment dyspnea, cough, and chest pain suggested a delay in time to development of or worsening of dyspnea, but not cough or chest pain, in patients treated with XALKORI as compared to chemotherapy. The patient-reported delay in onset or worsening of dyspnea may be an overestimation, because patients were not blinded to treatment assignment.

Table 12. Previously Untreated ALK-Positive Metastatic NSCLC - Efficacy Results in Study 1

	XALKORI (N=172)	Chemotherapy (N=171)
Progression-Free Survival (Based on IRR)		
Number of Events (%)	100 (58%)	137 (80%)
Progressive Disease	89 (52%)	132 (77%)
Death	11 (6%)	5 (3%)
Median, Months (95% CI)	10.9 (8.3, 13.9)	7.0 (6.8, 8.2)
HR (95% CI) ^a	0.45 (0.35, 0.60)	
p-value ^b	<0.001	
Overall Survival		
Number of Events (%)	71 (41%)	81 (47%)
Median, Months (95% CI)	NR (45.8, NR)	47.5 (32.2, NR)
HR (95% CI) ^a	0.76 (0.55, 1.05)	
p-value ^b	0.098	
Tumor Responses (Based on IRR)		
Objective Response Rate % (95% CI)	74% (67, 81)	45% (37, 53)
CR, n (%)	3 (1.7%)	2 (1.2%)
PR, n (%)	125 (73%)	75 (44%)
p-value ^c	<0.001	
Duration of Response		
Median, Months (95% CI)	11.3 (8.1, 13.8)	5.3 (4.1, 5.8)

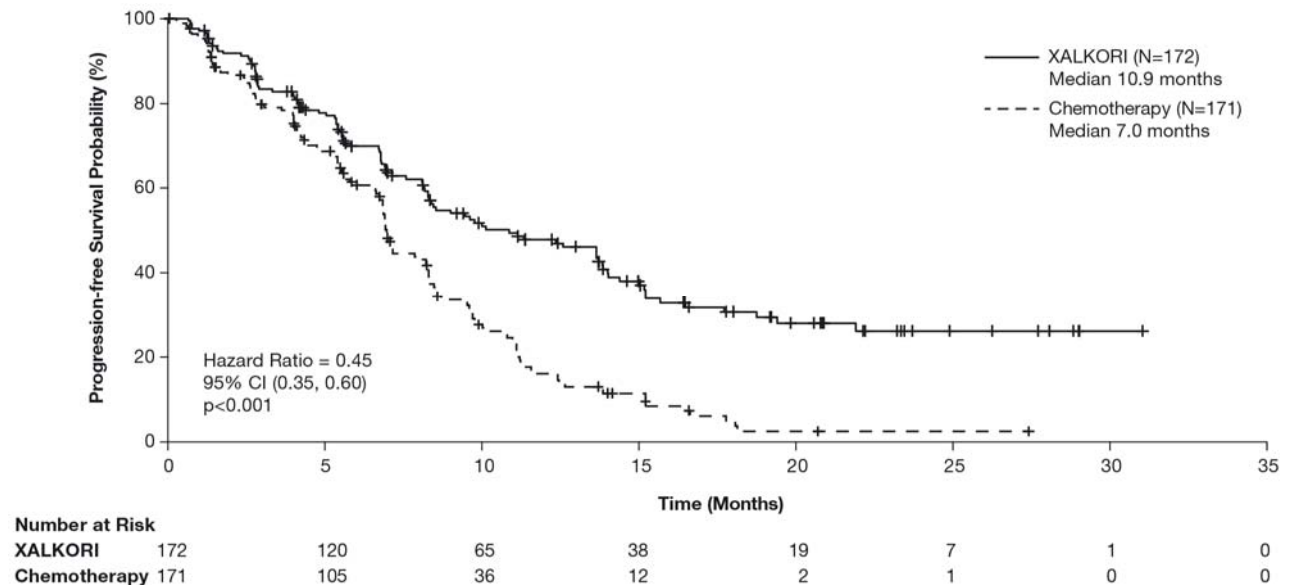
HR=hazard ratio; CI=confidence interval; IRR=independent radiology review; NR=not reached; CR=complete response; PR=partial response.

^a Based on the Cox proportional hazards stratified analysis.

^b Based on the stratified log-rank test.

^c Based on the stratified Cochran-Mantel-Haenszel test.

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



Previously Treated ALK-Positive Metastatic NSCLC - Study 2 (PROFILE 1007; NCT00932893)

The efficacy of XALKORI as monotherapy for the treatment of 347 patients with ALK-positive metastatic NSCLC, previously treated with 1 platinum-based chemotherapy regimen, were demonstrated in a randomized, multicenter, open-label, active-controlled study (Study 2). The major efficacy outcome was PFS according to RECIST version 1.1 as assessed by IRR. Additional efficacy outcomes included ORR as assessed by IRR, DOR, and OS.

Patients were randomized to receive XALKORI 250 mg orally twice daily (n=173) or chemotherapy (n=174). Chemotherapy consisted of pemetrexed 500 mg/m² (if pemetrexed-naïve; n=99) or docetaxel 75 mg/m² (n=72) intravenously (IV) every 21 days. Patients in both treatment arms continued treatment until documented disease progression, intolerance to therapy, or the investigator determined that the patient was no longer experiencing clinical benefit. Randomization was stratified by ECOG performance status (0-1, 2), brain metastases (present, absent), and prior EGFR tyrosine kinase inhibitor treatment (yes, no). Patients were required to have ALK-positive NSCLC as identified by the FDA-approved assay, Vysis ALK Break-Apart FISH Probe Kit, prior to randomization.

The demographic characteristics of the overall study population were 56% female, median age of 50 years, baseline ECOG performance status 0 or 1 (90%), 52% White and 45% Asian, 4% current smokers, 33% past smokers, and 63% never smokers. The disease characteristics of the overall study population were metastatic disease in at least 95% of patients and at least 93% of patients' tumors were classified as adenocarcinoma histology. At the time of the final analysis of overall survival, 89% of patients randomized to the chemotherapy arm subsequently received XALKORI.

Study 2 demonstrated a statistically significant improvement in PFS in the patients treated with XALKORI. Table 13 and Figure 2 summarize the efficacy results.

Table 13. Previously Treated ALK-Positive Metastatic NSCLC - Efficacy Results in Study 2

	XALKORI (N=173)	Chemotherapy (N=174)
Progression-Free Survival (Based on IRR)		
Number of Events (%)	100 (58%)	127 (73%)
Progressive Disease	84 (49%)	119 (68%)
Death	16 (9%)	8 (5%)
Median, Months (95% CI)	7.7 (6.0, 8.8)	3.0 ^a (2.6, 4.3)
HR (95% CI) ^b	0.49 (0.37, 0.64)	
p-value ^c	<0.001	
Overall Survival		
Number of Events (%)	116 (67%)	126 (72%)
Median, Months (95% CI)	21.7 (18.9,30.5)	21.9 (16.8,26.0)
HR (95% CI) ^b	0.85 (0.66, 1.10)	
p-value ^c	0.229	
Tumor Responses (Based on IRR)		
Objective Response Rate % (95% CI)	65% (58, 72)	20% (14, 26)
CR, n (%)	1 (0.6%)	0
PR, n (%)	112 (65%)	34 (20%)
p-value ^d	<0.001	
Duration of Response		
Median, Months (95% CI)	7.4 (6.1, 9.7)	5.6 (3.4, 8.3)

HR=hazard ratio; CI=confidence interval; IRR=independent radiology review; CR=complete response; PR=partial response.

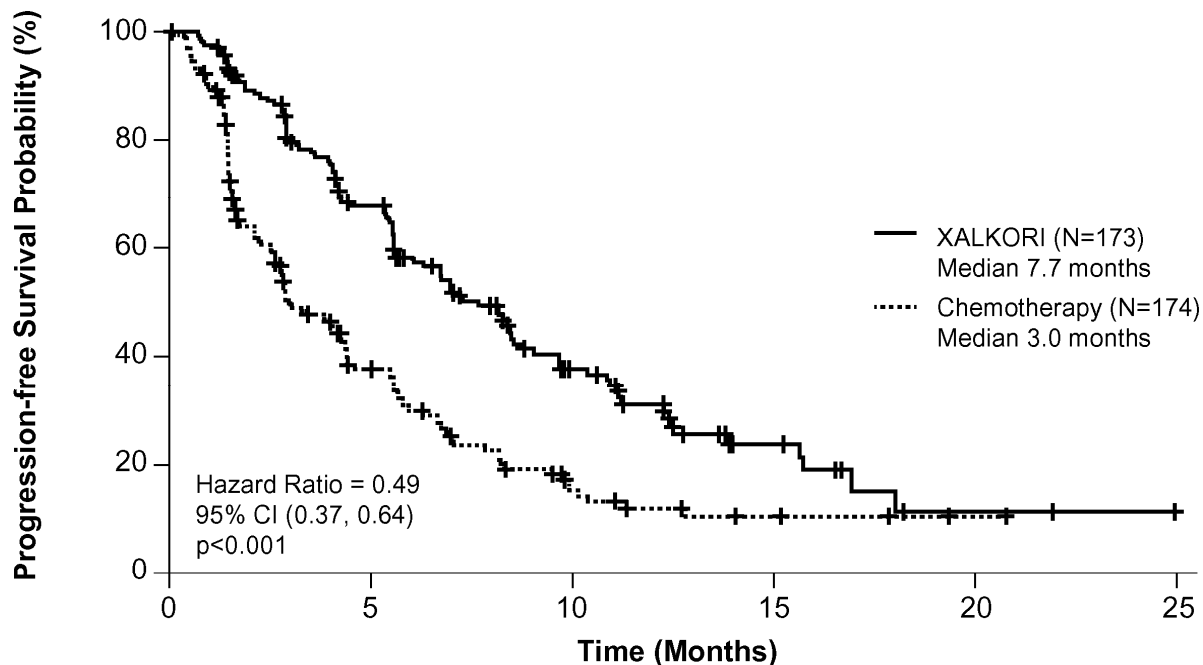
^a For pemetrexed, the median PFS was 4.2 months. For docetaxel, the median PFS was 2.6 months.

^b Based on the Cox proportional hazards stratified analysis.

^c Based on the stratified log-rank test.

^d Based on the stratified Cochran-Mantel-Haenszel test.

Figure 2. Kaplan-Meier Curves of Progression-Free Survival as Assessed by IRR in Study 2



Number at risk							
XALKORI	173	93	38	11	2	0	
Chemotherapy	174	49	15	4	1	0	

ROS1-Positive Metastatic NSCLC - Study 3 (PROFILE 1001; NCT00585195)

The efficacy and safety of XALKORI was investigated in a multicenter, single-arm study (Study 3), in which patients with ROS1-positive metastatic NSCLC received XALKORI 250 mg orally twice daily. Patients were required to have histologically-confirmed advanced NSCLC with a ROS1 rearrangement, age 18 years or older, ECOG performance status of 0, 1, or 2, and measurable disease. The efficacy outcome measures were ORR and DOR according to RECIST version 1.0 as assessed by IRR and investigator, with imaging performed every 8 weeks for the first 60 weeks.

Baseline demographic and disease characteristics were female (56%), median age of 53 years, baseline ECOG performance status of 0 or 1 (98%), White (54%), Asian (42%), past smokers (22%), never smokers (78%), metastatic disease (92%), adenocarcinoma (96%), no prior systemic therapy for metastatic disease (14%), and prior platinum-based chemotherapy for metastatic disease (80%). The ROS1 status of NSCLC tissue samples was determined by laboratory-developed break-apart FISH (96%) or RT-PCR (4%) clinical trial assays. For assessment by FISH, ROS1 positivity required that $\geq 15\%$ of a minimum of 50 evaluated nuclei contained a ROS1 gene rearrangement.

Efficacy results are summarized in Table 14.

Table 14. ROS1-Positive Metastatic NSCLC - Results* in Study 3

Efficacy Parameters	IRR (N=50)	Investigator-Assessed (N=50)
Objective Response Rate (95% CI)	66% (51, 79)	72% (58, 84)
Complete Response, n	1	5
Partial Response, n	32	31
Duration of Response		
Median, Months (95% CI)	18.3 (12.7, NR)	NR (14.5, NR)

IRR=independent radiology review; CI=confidence interval; NR=not reached.

*As assessed by RECIST version 1.0.

14.2 Relapsed or Refractory, Systemic ALK-Positive Anaplastic Large Cell Lymphoma

The efficacy of XALKORI was evaluated in Study ADVL0912 (NCT00939770), a multicenter, single arm, open-label study in patients 1 to ≤21 years of age that included 26 patients with relapsed or refractory, systemic ALK-positive ALCL after at least one systemic treatment. ALK positive status (confirmation of an ALK fusion) was determined locally by immunohistochemistry or fluorescence in situ hybridization. The study excluded patients with primary cutaneous ALCL or central nervous system involvement by lymphoma.

Patients received XALKORI 280 mg/m² (20 patients) or 165 mg/m² (6 patients) orally twice daily until disease progression or unacceptable toxicity. Patients were permitted to discontinue XALKORI to undergo hematopoietic stem cell transplantation (HSCT).

Of the 26 patients evaluated, the median age was 11 years (range: 3 to 20); 69% were male, 54% were White, 19% Black, 8% Asian. Patient enrollment by age category was 4 patients from 3 to <6 years, 11 patients from 6 to <12 years, 7 patients from 12 to <18 years, and 4 patients from 18 to ≤21 years.

All patients had received multi-agent systemic therapy, 2 (8%) had received a prior HSCT and 4 (15%) had received at least 3 prior therapies.

Efficacy was based on objective response rate and duration of response, as assessed by an independent review committee (Table 15). The median time to first response was 3.9 weeks (range: 3.5 to 9.1 weeks).

Table 15. Efficacy in Relapsed or Refractory, Systemic ALK-Positive ALCL

Efficacy Parameter	N=26
Objective response rate (95% CI, %)^{a,b}	88% (71, 96)
Complete response, n	21 (81%)
Partial response, n	2 (8%)
Duration of response^c	
Patients maintaining response at 3 months, n/N	13/23 (57%)
Patients maintaining response at 6 months, n/N	9/23 (39%)
Patients maintaining response at 12 months, n/N	5/23 (22%)

CI=confidence interval; N/n=number of patients

^a Based on Lugano Classification.

^b 95% CI based on Wilson score method.

^c Of 23 patients with objective response, 2 had disease progression and the remainder (91% of responding patients) were censored.

16 HOW SUPPLIED/STORAGE AND HANDLING

- 250 mg capsules
Hard gelatin capsule with pink opaque cap and body, printed with black ink “Pfizer” on the cap, “CRZ 250” on the body; available in:
Bottles of 60 capsules: NDC 0069-8140-20
- 200 mg capsules
Hard gelatin capsule with pink opaque cap and white opaque body, printed with black ink “Pfizer” on the cap, “CRZ 200” on the body; available in:
Bottles of 60 capsules: NDC 0069-8141-20

Store at room temperature 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Hepatotoxicity

Inform patients to immediately report symptoms of hepatotoxicity [see *Warnings and Precautions (5.1)*].

Interstitial Lung Disease (Pneumonitis)

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

Bradycardia

Advise patients to report any symptoms of bradycardia and to inform their healthcare provider about the use of any heart or blood pressure medications [see *Warnings and Precautions (5.4)*].

Severe Visual Loss

Inform patients of the potential risk of severe visual loss and to immediately contact their healthcare provider if they develop severe visual loss. Inform patients that visual changes such as perceived flashes of light, blurry vision, light sensitivity, and floaters are commonly reported adverse reactions and may occur while driving or operating machinery. The onset of visual disorders most commonly occurs during the first week of treatment [see *Warnings and Precautions (5.5)*, *Adverse Reactions (6)*].

Gastrointestinal Toxicity in Patients with ALCL

Inform patients with ALCL of the risk of severe nausea, vomiting, diarrhea, and stomatitis. Advise patients to immediately inform their healthcare provider of problems with swallowing, vomiting, or diarrhea [see *Warnings and Precautions (5.6)*].

Drug Interactions

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

Photosensitivity

Inform patients of the signs and symptoms of photosensitivity. Advise patients to avoid prolonged sun exposure and to use sunscreen or protective clothing during treatment with XALKORI [see *Adverse Reactions (6.1)*].

Dosage and Administration

Advise patients to take XALKORI with or without food and to swallow XALKORI capsules whole. If a patient misses a dose, advise the patient to take it as soon as remembered unless it is less than 6 hours until the next dose, in which case, advise the patient not to take the missed dose. If a patient vomits after taking a dose of XALKORI, advise the patient not to take an extra dose, but to take the next dose at the regular time.

Embryo-Fetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy [see *Warnings and Precautions (5.7), Use in Specific Populations (8.1)*].

Females and Males of Reproductive Potential

Advise females of reproductive potential to use effective contraception during treatment with XALKORI and for at least 45 days after the final dose [see *Use in Specific Populations (8.3)*].

Advise males with female partners of reproductive potential to use condoms during treatment with XALKORI and for at least 90 days after the final dose [see *Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)*].

Lactation

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

Infertility

Advise females and males of reproductive potential of the potential for reduced fertility from XALKORI [see *Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)*].

This product's labeling may have been updated. For the most recent prescribing information, please visit www.XALKORI.com.



MEDICATION GUIDE
XALKORI® (zal-KOR-ee)
(crizotinib)
capsules

What is the most important information I should know about XALKORI?

XALKORI may cause serious side effects, including:

- **Liver problems.** XALKORI may cause life-threatening liver injury that may lead to death. Your healthcare provider should do blood tests to check your liver every 2 weeks during the first 2 months of treatment with XALKORI, then once a month and as recommended by your healthcare provider during treatment. Tell your healthcare provider right away if you develop any of the following new or worsening symptoms:
 - yellowing of your skin or the white part of your eyes
 - severe tiredness
 - dark or brown (tea color) urine
 - nausea or vomiting
 - decreased appetite
 - pain on the right side of your stomach
 - bleed or bruise more easily than normal
 - itching
 - **Lung problems (pneumonitis).** XALKORI may cause life-threatening lung problems that may lead to death. Symptoms may be similar to those symptoms from lung cancer. Tell your healthcare provider right away if you have any new or worsening symptoms, including:
 - trouble breathing or shortness of breath
 - cough with or without mucous
 - fever
 - **Heart problems.** XALKORI may cause very slow, very fast, or abnormal heartbeats. Your healthcare provider may check your pulse rate and blood pressure regularly during treatment with XALKORI. Tell your healthcare provider right away if you feel dizzy or faint or have abnormal heartbeats. Tell your healthcare provider if you take any heart or blood pressure medicines.
 - **Severe vision problems.** Vision problems are common with XALKORI. These problems usually happen within 1 week of starting treatment with XALKORI. Vision problems with XALKORI can be severe and may cause partial or complete loss of vision in one or both eyes. Your healthcare provider may hold or permanently stop your treatment with XALKORI and refer you to an eye specialist if any vision problems develop during treatment with XALKORI. Tell your healthcare provider right away if you have any new vision problems, loss of vision or any change in vision, including:
 - double vision
 - seeing flashes of light
 - blurry vision
 - light hurting your eyes
 - new or increased floaters
- In addition, for people taking XALKORI to treat anaplastic large cell lymphoma (ALCL): Your healthcare provider may refer you to an eye specialist before starting XALKORI, and within 1 month of starting XALKORI to check for vision problems. You should have an eye examination every 3 months during treatment with XALKORI and more often if there are any new vision problems.
- **Severe stomach, intestine, and mouth (gastrointestinal) problems in people with ALCL.** XALKORI may cause severe diarrhea, nausea, vomiting, or mouth sores. Tell your healthcare provider right away if problems with swallowing, vomiting, or diarrhea develop during treatment with XALKORI.
 - Your healthcare provider may give medicines as needed to prevent or treat diarrhea, nausea, and vomiting.
 - Your healthcare provider may recommend drinking more fluids or may prescribe electrolyte supplements or other kinds of nutritional support if severe symptoms develop.

See “What are possible side effects of XALKORI?” for more information about side effects.

What is XALKORI?

XALKORI is a prescription medicine that is used to treat:

- people with non-small cell lung cancer (NSCLC) that has spread to other parts of the body and is caused by a defect in either a gene called ALK (anaplastic lymphoma kinase) or a gene called ROS1.
- children 1 year of age and older and young adults when your ALCL with a defect in a gene called ALK has returned, or you have tried a treatment and it did not work or is no longer working.

It is not known if XALKORI is safe and effective in children under 12 months of age or in older adults with ALCL.

Before taking XALKORI, tell your healthcare provider about all of your medical conditions, including if you:

- have liver or kidney problems
- have lung problems

- have heart problems, including a condition called long QT syndrome
- have vision or eye problems
- are pregnant, or plan to become pregnant. XALKORI can harm the unborn baby.

Females who are able to become pregnant:

- Your healthcare provider will check to see if you are pregnant before starting treatment with XALKORI.
- Effective birth control (contraception) should be used during treatment with XALKORI and for at least 45 days after the final dose of XALKORI.
- Tell your healthcare provider right away if you become pregnant or think you might be pregnant during treatment with XALKORI.

Males who have female partners who can become pregnant:

- You should use condoms during treatment with XALKORI and for at least 90 days after the final dose of XALKORI.
- are breastfeeding or plan to breastfeed. It is not known if XALKORI passes into the breast milk. Do not breastfeed during treatment with XALKORI and for 45 days after the final dose. Talk to your healthcare provider about the best way to feed the baby during this time.

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

How should I take XALKORI?

- XALKORI should be taken exactly as prescribed by your healthcare provider.
- XALKORI capsules should be swallowed whole.
- XALKORI may be taken with or without food.
- Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with XALKORI if you have certain side effects. Do not change the dose or stop treatment with XALKORI unless your healthcare provider tells you to.
- If a dose of XALKORI is missed, it should be taken as soon as you remember. If it is close to the time of the next dose (within 6 hours), the missed dose should be skipped, and the next dose should be taken at the regular time.
- If you vomit after taking a dose of XALKORI, do not take an extra dose. The next dose should be taken at the regular time.
- XALKORI should be given to children under adult supervision.

What should I avoid while taking XALKORI?

- Do not drink grapefruit juice, eat grapefruit or take supplements containing grapefruit extract during treatment with XALKORI. These may increase the amount of XALKORI in the blood.
- XALKORI can cause changes in vision, dizziness, and tiredness. Do not drive or operate machinery if you have any of these symptoms.
- Avoid spending prolonged time in sunlight. XALKORI can make your skin sensitive to the sun (photosensitivity), and you may burn more easily. You should use sunscreen and wear protective clothing that covers your skin to help protect against sunburn if you have to be in the sunlight during treatment with XALKORI.

What are the possible side effects of XALKORI?

XALKORI may cause serious side effects, including:

- See “What is the most important information I should know about XALKORI?”

The most common side effects of XALKORI in people with NSCLC include:

- | | |
|--|--|
| • vision problems | • tiredness |
| • nausea, diarrhea, or vomiting | • decreased appetite |
| • swelling of your hands, feet, face, and eyes | • upper respiratory infection |
| • constipation | • dizziness |
| • increased liver function blood tests | • feeling of numbness or tingling in your arms or legs |

The most common side effects of XALKORI in people with ALCL include:

- | | |
|---------------------------------|---------------------------------|
| • diarrhea, vomiting, or nausea | • stomach-area (abdominal) pain |
| • vision problems | • cough |
| • headache | • itchy skin |

- muscle and joint pain
- mouth sores
- tiredness
- decreased appetite
- fever
- low blood counts
- abnormal liver tests
- low levels of electrolytes
- abnormal kidney tests
- low and high blood sugar levels

XALKORI may cause fertility problems in females and males, which may affect the ability to have children. Talk to your healthcare provider if you have concerns about fertility.

These are not all of the possible side effects of XALKORI.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store XALKORI?

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

Keep XALKORI and all medicines out of the reach of children.

General information about the safe and effective use of XALKORI.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use XALKORI for a condition for which it was not prescribed. Do not give XALKORI to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for more information about XALKORI that is written for health professionals.

What are the ingredients in XALKORI?

Active ingredient: crizotinib

Inactive ingredients: colloidal silicon dioxide, microcrystalline cellulose, anhydrous dibasic calcium phosphate, sodium starch glycolate, and magnesium stearate.

Pink opaque capsule shell contains: gelatin, titanium dioxide, and red iron oxide.

White opaque capsule shell contains: gelatin and titanium dioxide.

Printing ink contains: shellac, propylene glycol, strong ammonia solution, potassium hydroxide, and black iron oxide.



LAB-0441-9.3

For more information, go to www.XALKORI.com or call 1-800-438-1985.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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