PRODUCT MONOGRAPH

Pr XALKORI®

Crizotinib Capsules

200 mg and 250 mg capsules

Anaplastic Lymphoma Kinase (ALK) Tyrosine Kinase Inhibitor

XALKORI (crizotinib), indicated as monotherapy for use in patients with anaplastic lymphoma kinase (ALK)-positive locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC), has been issued marketing authorization with conditions, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the authorization.

Pfizer Canada Inc.
17300 Trans-Canada Highway
Kirkland, Quebec
H9J 2M5

Date of Revision:
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Submission Control No: 178840

This product has been approved under the Notice of Compliance with Conditions (NOC/c) policy for one or all of its indicated uses.

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products approved under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

What will be different about this Product Monograph?

The following Product Monograph will contain boxed text at the beginning of each major section clearly stating the nature of the market authorization. Sections for which NOC/c status holds particular significance will be identified in the left margin by the symbol NOC/c. These sections may include, but are not limited to, the following:

- Indications and Clinical Uses;
- Action;
- Warnings and Precautions;
- Adverse Reactions;
- Dosage and Administration; and
- Clinical Trials.

Adverse Drug Reaction Reporting and Re-Issuance of the Product Monograph

Health care providers are encouraged to report Adverse Drug Reactions associated with normal use of these and all drug products to Health Canada's Health Product Safety Information Division at 1-866-234-2345. The Product Monograph will be re-issued in the event of serious safety concerns previously unidentified or at such time as the sponsor provides the additional data in support of the product's clinical benefit. Once the latter has occurred, and in accordance with the NOC/c policy, the conditions associated with market authorization will be removed.

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PART I: HEALTH PROFESSIONAL INFORMATION

XALKORI (crizotinib), indicated as monotherapy for use in patients with anaplastic lymphoma kinase (ALK)-positive locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC), has been issued marketing authorization with conditions, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the authorization.

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	capsules 200 mg and 250 mg	No clinically relevant nonmedicinal ingredients. *For a complete listing see Dosage Forms, Composition and Packaging section*.

NOC/c

INDICATIONS AND CLINICAL USE

XALKORI (crizotinib) is indicated as monotherapy for use in patients with anaplastic lymphoma kinase (ALK)-positive locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC).

Using a validated ALK assay, assessment for ALK-positive locally advanced or metastatic NSCLC should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. Improper assay performance can lead to unreliable test results (see CLINICAL TRIALS section). ALK gene rearrangements were identified in Study A8081001 by clinical trial assays performed by local laboratories and in most patients from Study A8081005 and all patients from Study A8081007 by a Health Canada-approved Vysis ALK break-apart fluorescence in situ hybridization (FISH) assay. The clinical benefit of XALKORI in patients with anaplastic lymphoma kinase (ALK)-negative NSCLC has not been established; therefore, XALKORI is not recommended for these patients.

Marketing authorization with conditions was based on a primary efficacy endpoint of objective response rate (ORR) as well as duration of response (DR) in clinical Studies A8081001 and A8081005, based on investigator assessment using RECIST (see CLINICAL TRIALS). There are no data available demonstrating improvement in survival with XALKORI.

Geriatrics (≥65 years of age):
Of the 172 XALKORI-treated patients in Study A8081007, 27 (16%) were 65 years or older. Of the 119 patients in Study A8081001, 16 (13%) were 65 years or older. Of the 934 patients in Study A8081005, 152 (16%) were 65 years or older. No overall differences in safety or effectiveness were observed between younger and older patients.

Pediatrics (<18 years of age):
The safety and efficacy of crizotinib in pediatric patients have not been established.

NOC/c CONTRAINDICATIONS

Patients with congenital long QT syndrome or with a persistent Fridericia-corrected electrocardiogram interval (QTcF) of ≥500 msec (see WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS).

Patients with a known hypersensitivity to the active substance, crizotinib, or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.

NOC/c WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- QT interval prolongation and bradycardia. (See Warnings and Precautions, Adverse Reactions)
- Hepatotoxicity, including fatal outcomes. (See Warnings and Precautions, Adverse Reactions)
- XALKORI has not been studied in patients with hepatic impairment or severe renal impairment requiring peritoneal dialysis or hemodialysis. (See Warnings and Precautions, Adverse Reactions)
- Interstitial Lung Disease (Pneumonitis), including fatal cases. (See Warnings and Precautions, Adverse Reactions)

XALKORI (crizotinib) should only be prescribed and supervised by a qualified physician experienced in the use of anticancer agents.

General

ALK Testing

Prior to receiving therapy with XALKORI, patients must be tested and confirmed for ALK-positive locally advanced or metastatic NSCLC using a validated ALK assay (see CLINICAL TRIALS section). Assessment for ALK-positive locally advanced or metastatic NSCLC should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. Improper assay performance can lead to unreliable test results. The clinical benefit of XALKORI in patients with ALK-negative NSCLC has not been established.

Drug Interactions

Crizotinib is a substrate and inhibitor of CYP3A. The concurrent use of strong CYP3A inhibitors such as ketoconazole may increase crizotinib plasma concentration and should be avoided. The concurrent use of strong CYP3A inducers such as rifampin may decrease crizotinib plasma concentration and should be avoided. The concurrent use of CYP3A substrates with narrow therapeutic indices and associated with life-threatening arrhythmias such as pimozide should be avoided (see DOSAGE AND ADMINISTRATION and DRUG INTERACTIONS).

Missed Dose

If a dose of crizotinib is missed, then it should be taken as soon as possible. If it is less than 6 hours until the next dose, then the patient should not take the missed dose. Patients should not take 2 doses at the same time to make up for a missed dose.

Effects on Ability to Drive and Use Machinery

Vision disorder, most commonly visual impairment, photopsia, vision blurred, and vitreous floaters, was experienced by 101 (59%) patients in Study A8081007, 74 (62%) patients in Study A8081001, and 496 (53%) patients in Study A8081005. Caution should be exercised when driving or operating machinery by patients who experience vision disorders (see DRUG INTERACTIONS).

Carcinogenesis and Mutagenesis

Crizotinib was genotoxic in non-clinical studies (see PART II, TOXICOLOGY; Carcinogenesis, Mutagenesis, Phototoxicity, Reproductive and Developmental Toxicity). Carcinogenicity studies with crizotinib have not been performed.

Cardiovascular

Bradycardia

Treatment-emergent bradycardia was reported in clinical studies in 5 to 14% of patients treated with crizotinib. The full effect on reduction of heart rate may not develop until several weeks after start of treatment. Symptomatic bradycardia (e.g. syncope, dizziness, hypotension) can occur in patients receiving XALKORI (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests; ADVERSE REACTIONS, Electrocardiography and Haemodynamics). Caution should be exercised in patients with a low heart rate at baseline (<60 beats per minute), a

history of syncope or arrhythmia, sick sinus syndrome, sinoatrial block, atrioventricular (AV) block, ischemic heart disease, or congestive heart failure. Avoid using crizotinib in combination with other bradycardic agents (e.g., beta-blockers, non-dihydropyridine calcium channel blockers such as verapamil and diltiazem, clonidine, digoxin) to the extent possible, due to the increased risk of symptomatic bradycardia. Monitor heart rate and blood pressure regularly (see Monitoring and Laboratory Tests).

Permanently discontinue for life-threatening symptomatic bradycardia due to XALKORI. If contributing concomitant medication is identified and discontinued, hold XALKORI until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. Dose modification is not required in cases of asymptomatic bradycardia. For management of patients who develop symptomatic bradycardia, see DOSAGE AND ADMINISTRATION and Monitoring and Laboratory Tests.

QT Interval Prolongation
Prolongation of corrected QT interval without accompanying arrhythmia has been observed (see Electrocardiography and Hemodynamics, ADVERSE REACTIONS). Pharmacokinetic/pharmacodynamic modeling indicated a concentration-dependent increase in QTcF and decrease in heart rate (HR) (see Electrocardiography and Hemodynamics, ADVERSE REACTIONS). XALKORI should be administered with caution to patients who have a history of, or a predisposition for QTc prolongation, or who are taking medications that are known to prolong the QT interval. When using XALKORI, periodic monitoring of electrocardiogram (ECG) QTc and electrolytes should be considered. In the event of a QTc ≥500 msec (Grade 3), dosing with XALKORI should be withheld until recovery to Grade ≤1 (≤470 msec), then resumed at a reduced dose of 200 mg twice daily. Permanent discontinuation of XALKORI is recommended in the event of a Grade 4 QTc prolongation (≥500 msec [or >60 msec change from baseline] and Torsade de Pointes or polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmias) (see Dose Modification and ADVERSE REACTIONS Sections).

QTc prolongation may lead to an increased risk of ventricular arrhythmias including Torsade de Pointes. Torsade de Pointes is a polymorphic ventricular tachyarrhythmia. Generally, the risk of Torsade de Pointes increases with the magnitude of QTc prolongation produced by the drug. Torsade de Pointes may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, Torsade de Pointes can progress to ventricular fibrillation and sudden cardiac death. Treatment with XALKORI is not recommended in patients with congenital long QT syndrome, or who are taking medicinal products known to prolong the QT interval (see DRUG INTERACTIONS). Hypokalemia, hypomagnesemia, and hypocalcemia must be corrected prior to XALKORI administration.

Particular care should be exercised when administering XALKORI to patients who are suspected to be at an increased risk of experiencing Torsade de Pointes during treatment with a QTc-prolonging drug.

Risk factors for Torsade de Pointes in the general population include, but are not limited to, the following: female gender; age ≥65 years; baseline prolongation of the QT/QTc interval; presence of genetic variants affecting cardiac ion channels or regulatory proteins, especially congenital long QT syndromes; family history of sudden cardiac death at <50 years of age; cardiac disease; history of arrhythmias; electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypocalcemia); bradycardia; acute neurological events (e.g., intracranial or subarachnoid haemorrhage, stroke, intracranial trauma); nutritional deficits; diabetes mellitus; and autonomic neuropathy.

When drugs that prolong the QT/QTc interval are prescribed, healthcare professionals should counsel their patients concerning the nature and implications of the ECG changes, underlying diseases and disorders that are considered to represent risk factors, demonstrated and predicted drug-drug interactions, symptoms suggestive of arrhythmia, risk management strategies, and other information relevant to the use of the drug.

Crizotinib is a functional antagonist of sodium, potassium, and calcium currents (see Safety Pharmacology).

Thrombotic Events
Deep vein thrombosis was observed in 34 patients (3%) [3 (1.7%) in Study A8081007, 27 (2.9%) in Study A8081005, and 4 (3.4%) from Study A8081001]. Grade 5 treatment-related adverse events of disseminated intravascular coagulation and arteriosclerotic cardiovascular disease occurred in 2 patients (<1%) (1 patient each) (see ADVERSE REACTIONS). XALKORI should be used with caution in patients who are at increased risk of thrombotic events. XALKORI has not been studied in patients who have had myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, congestive heart failure, or cerebrovascular accident including transient ischemic attack within the previous 3 months.

Cardiac Dysfunction
Some tyrosine kinase inhibitors have been associated with cardiomyopathy, decreased ventricular performance, and heart failure. The results of left ventricular ejection fraction (LVEF) monitoring with XALKORI are pending. Patients receiving XALKORI should be monitored for signs and symptoms of heart failure such as edema, dyspnea, and chest pain. XALKORI has been associated with edema and dyspnea in clinical trials (see ADVERSE REACTIONS). Consideration should be given to the use of cardiac imaging methodologies to monitor cardiac function during XALKORI treatment.

Gastrointestinal
Nausea (51% [59/119 (50%) in Study A8081001, 476/934 (51%) in Study A8081005, and 94/172 (55%) in Study A8081007]), diarrhea (48% [57/119 (48%) in Study A8081001, 432/934 (46%) in Study A8081005, and 103/172 (60%) in Study A8081007]), vomiting (46% [48/119 (40%) in Study A8081001, 433/934 (46%) in Study A8081005, and 80/172 (47%) in Study A8081007]), and constipation (39% [45/119 (38%) in Study A8081001, 356/934 (38%) in Study A8081005, and 73/172 (42%) in Study A8081007]) were the most commonly reported gastrointestinal events (see ADVERSE REACTIONS). Median times to onset for nausea and

vomiting was 2 to 3 days across Studies A8081007, A8081001, and A8081005. Most events were mild to moderate in severity, and declined in frequency after 3 to 4 weeks of treatment. Supportive care may include the use of antiemetic medications. In clinical trials, the most commonly used antiemetic medications were ondansetron and prochlorperazine. Diarrhea and constipation were primarily mild to moderate in severity. Supportive care for diarrhea and constipation may include the use of standard antidiarrheal and laxative medications, respectively.

Hepatic/Biliary/Pancreatic

Hepatotoxicity, including hepatic failure, with fatal outcome has occurred in 1.6% patients treated with crizotinib in clinical trials (ranging from 0 to 2.9% across the individual clinical trials [0/119 (0%) in Study A8081001, 14/934 (1.5%) in Study A8081005, and 5/172 (2.9%) in Study A8081007]). Concurrent elevations in ALT >3 x ULN and total bilirubin >2 x ULN without elevated alkaline phosphatase (Hy's Law) have been observed in <1% of patients in clinical trials. Grade 3 or 4 ALT elevation was observed in 17% of patients in Study A8081007, 4% patients in Study A8081001 and 8% of patients in Study A8081005. Grade 3 and 4 elevations were generally asymptomatic and reversible upon dosing interruption. Patients usually resumed treatment at a lower dose without recurrence; however, 2 patients from Study A8081007 (1%), 1 (<1%) patient from Study A8081001 and 5 (<1%) patients from Study A8081005 required permanent discontinuation from treatment. Transaminase elevations generally occurred within the first 2 months of XALKORI treatment. Monitor with liver function tests including ALT and total bilirubin every 2 weeks during the first 2 months of treatment, then once a month and as clinically indicated, with more frequent repeat testing for Grades 2, 3 or 4 elevation in patients who develop transaminase elevations (see DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS).

Neurologic

Neuropathy (motor and sensory, see Table 1) was experienced by 33/172 (19%) of patients in randomized Phase 3 Study A8081007, 24/119 (20%) patients in Study A8081001 and 178/934 (19%) patients in Study A8081005, and was mainly Grade 1 in severity. Dizziness (20%) and dysgeusia (19%) were also commonly reported in these studies, and were primarily Grade 1 in severity. CNS haemorrhage has been reported in 2 (<1%) patients treated with crizotinib, both of whom were pediatric patients with previously treated primary intracranial tumors, 1 of whom had a fatal outcome (see Non Clinical Secondary Pharmacodynamics section).

Ophthalmologic

Vision disorder, most commonly visual impairment, photopsia, vision blurred, and vitreous floaters, was experienced by 103 (60%) patients in Study A8081007, 75 (63%) patients in Study A8081001, and 513 (55%) patients in Study A8081005. Greater than 95% of these patients had events that were mild in severity with median time to onset of 5 days, 13 days, and 7 days in Studies A8081007, A8081001 and A8081005, respectively. None of the patients in Studies A8081007, A8081001 and A8081005 required dosing interruption, dose reduction, or permanent discontinuation from study treatment for vision disorder, except 1 patient from Study A8081001 and 4 patients from Study A8081005 who had temporary treatment discontinuation and 1 patient from Study A8081005 and 1 patient from Study A8081007 who had dose reduction for vision disorder. Ophthalmological evaluation should be considered if vision disorder persists or worsens in severity. Caution should be exercised when driving or operating machinery by patients who experience vision disorder (see Non Clinical Toxicology section).

Renal

Renal cyst was most commonly complex, and has been reported in 7 (4%) patients in randomized Phase 3 Study A8081007, and 0 and 12 (1%) patients in Studies A8081001 and A8081005, respectively. There were no reports of clinically relevant abnormal urinalyses or renal impairment in these cases, although local invasion beyond the kidney was observed in some patients. The significance is unknown (see ADVERSE REACTIONS). Periodic monitoring with imaging and urinalysis should be considered in patients who develop renal cysts.

Respiratory

Interstitial Lung Disease/Pneumonitis

XALKORI has been associated with severe, life-threatening or fatal interstitial lung disease (ILD)/pneumonitis in clinical trials with a frequency of 32 in 1225 (3%) patients across Studies A8081007 (4%), A8081001 (3%) and A8081005 (2%). These cases generally occurred within 2 months after the initiation of treatment. Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis. Other potential causes of ILD/pneumonitis should be excluded, and XALKORI should be interrupted during these investigations. XALKORI should be permanently discontinued in patients diagnosed with treatment-related ILD/pneumonitis (see DOSAGE AND ADMINISTRATION, Dose Modifications and ADVERSE REACTIONS sections).

Sexual Function/Reproduction

Fertility

Based on reproductive organ findings in toxicology studies, male and female fertility may be impaired by treatment with crizotinib (see PART II, TOXICOLOGY; Animal Toxicology section).

Special Populations

Pregnant Women
There are no adequate and well-controlled studies in pregnant women using XALKORI. XALKORI may cause fetal harm when administered to a pregnant woman. Crizotinib was shown to be fetotoxic but not teratogenic in pregnant rats and rabbits (see PART II TOXICOLOGY, Carcinogenesis, Mutagenesis, Phototoxicity, Reproductive and Developmental Toxicity).

Women of childbearing potential should be advised to avoid becoming pregnant while receiving XALKORI. Adequate contraceptive methods should be used during therapy, and for at least 90 days after completing therapy.

If XALKORI is used during pregnancy, or if the patient or their partner becomes pregnant while receiving XALKORI, then the patient or their partner should be apprised of the potential hazard to the fetus or potential risk for loss of the pregnancy.

Nursing Women
There are no adequate and well-controlled studies in nursing women using XALKORI. It is not known whether crizotinib and its metabolites are excreted in human milk. Because many drugs are commonly excreted in human milk, and because of the potential harm to nursing infants due to exposure to crizotinib, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother (see PART II, TOXICOLOGY section).

Male Patients
Adequate contraceptive methods should be used by men during therapy, and for at least 90 days after completing therapy. If the patient's partner becomes pregnant while receiving XALKORI, then the patient and his partner should be apprised of the potential hazard to the fetus or potential risk for loss of the pregnancy.

Pediatrics (<18 years of age)
The safety and efficacy of XALKORI in pediatric patients have not been established. In toxicology studies, decreased bone formation in growing long bones was observed in immature rats (see PART II, TOXICOLOGY; Animal Toxicology). Other toxicities of potential concern to pediatric patients have not been evaluated in juvenile animals.

Geriatrics (≥65 years of age)
Of the 172 crizotinib-treated patients in Study A8081007, 27 (16%) were 65 years or older. Of the 119 patients in Study A8081001, 16 (13%) were 65 years or older. Of the 934 patients in Study A8081005, 152 (16%) were 65 years or older. Based on existing data, no overall differences in safety or efficacy were observed between younger and older patients.

Hepatic Impairment
XALKORI has not been studied in patients with hepatic impairment. Clinical studies excluded patients with AST or ALT >2.5 x ULN or, >5.0 x ULN if due to underlying malignancy, or with

total bilirubin >1.5 x ULN. As XALKORI is extensively metabolized in liver, hepatic impairment may result in higher plasma concentrations. Treatment with XALKORI should be used with caution in patients with hepatic impairment (see DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS and ACTION AND CLINICAL PHARMACOLOGY sections).

Renal Impairment
Based on a PK study, the starting dose of XALKORI should be reduced by 50% (250 mg once daily) in patients with severe renal impairment (CLcr < 30 mL/min) not requiring peritoneal dialysis or hemodialysis. No starting dose adjustment is recommended for patients with mild (CLcr 60-89mL/min) or moderate (CLcr 30-59 mL/min) renal impairment, although data are limited. Patients with mild or moderate renal impairment should be treated with caution (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY Special Populations and Conditions, Renal Impairment).

No data available for patients with severe renal impairment requiring peritoneal dialysis or hemodialysis (CLcr < 30 mL/min) (see WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions).

Monitoring and Laboratory Tests

ALK Testing
Prior to receiving therapy with XALKORI, patients must be tested and confirmed for ALK-positive locally advanced or metastatic NSCLC using a validated ALK assay (see CLINICAL STUDIES section). Assessment for ALK-positive locally advanced NSCLC should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. Improper assay performance can lead to unreliable test results. The clinical benefit of XALKORI in NSCLC patients with ALK-negative tumors has not been established.

Renal Monitoring
Creatinine levels should be assessed at baseline and monitored periodically during treatment with XALKORI.

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

Liver Function Test Monitoring
Liver function tests including ALT and total bilirubin should be performed before XALKORI administration and monitored every 2 weeks during the first 2 months of treatment, then once a month and as clinically indicated, with more frequent repeat testing for Grades 2, 3 or 4 elevation. In patients who develop transaminase elevations, consult Dose Modification section (see DOSAGE AND ADMINISTRATION section).

Cardiac Safety Monitoring
Patients receiving XALKORI should be monitored for heart rate and blood pressure. ECG evaluations should be performed at baseline prior to initiating therapy with XALKORI and should be repeated periodically during treatment with XALKORI, to monitor for decreased heart rate and QTc prolongation (see WARNINGS AND PRECAUTIONS, Cardiovascular; ADVERSE REACTIONS, Electrocardiography and Haemodynamics; DRUG INTERACTIONS). Consultation with a cardiologist should be considered when assessing the QT interval to ensure appropriate treatment decisions.

Electrolyte levels (calcium, potassium, and magnesium) should be assessed at baseline and monitored periodically during treatment with XALKORI, particularly in patients at risk for these electrolyte abnormalities (see WARNINGS AND PRECAUTIONS, Cardiovascular; DRUG INTERACTIONS). Hypocalcemia, hypokalemia, and hypomagnesemia should be corrected prior to XALKORI administration.

ADVERSE REACTIONS

NOC/c

Adverse Drug Reaction Overview

The data described below reflect exposure to XALKORI in 172 patients with ALK-positive advanced NSCLC who participated in a randomized Phase 3 study (Study A8081007) and in 1053 patients with ALK-positive NSCLC who participated in 2 single-arm clinical trials (Studies A8081001 and A8081005). These patients received a starting oral dose of 250 mg taken twice daily continuously.

The most serious adverse drug reactions in patients with ALK-positive advanced NSCLC are hepatotoxicity, ILD/pneumonitis, and QT interval prolongation (see WARNINGS AND PRECAUTIONS). The most common adverse drug reactions (≥10%) in patients with ALK-positive NSCLC were vision disorder (56%), nausea (51%), diarrhea (48%), vomiting (46%), constipation (39%), edema (38%), fatigue (26%), elevated transaminases (25%), decreased appetite (25%), dizziness (20%), cough (19%), neuropathy (20%), dysguesia (19%), dyspnea (19%), upper respiratory infection (18%), abdominal pain (15%), neutropenia (15%), headache (13%), pyrexia (13%), stomatitis (12%), chest pain (11%), back pain (11%), anemia (11%) and rash (10%). Treatment-emergent all-causality bradycardia was experienced by 8 (5%) patients in randomized Phase 3 Study A8081007, and 8 (7%) and 57 (6%) patients in Studies A8081001 and A8081005, respectively. The majority of these cases were Grade 1 or 2 in severity. In Studies A8081007, A8081001, and A8081005, 19 of 170 (11%) patients, 16 of 114 (14%) patients, and 90 of 890 (10%) patients had a pulse heart rate <50 bpm.

Across all XALKORI clinical studies, 1445 patients have received XALKORI at a starting dose of 250 mg twice daily across various tumor types, the most common being NSCLC. The safety profile for these patients was consistent with that observed for the 1225 patients with ALK-positive NSCLC.

Clinical Trial Adverse Drug Reactions

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

Randomized Phase 3 Study (Study A8081007)

The safety analysis population in Study A8081007 included 172 patients who received XALKORI and 171 patients who received chemotherapy (99 pemetrexed, 72 docetaxel). The median duration of study treatment was 31 weeks for patients on XALKORI and 12 weeks for patients on chemotherapy (18 weeks for pemetrexed and 9 weeks for docetaxel). Serious adverse events occurred in 64 (37%) patients on XALKORI, the most common of which were disease progression, pneumonia, pulmonary embolism and dyspnoea and 40 (23%) patients on chemotherapy, the most common of which was febrile neutropenia. Grade 5 events occurred in 25 (15%) patients on XALKORI, the most common of which was disease progression and 7 (4%) patients on chemotherapy, the most common of which was disease progression. Dosing interruptions due to adverse events occurred in 67 (39%) patients on XALKORI, the most common of which were neutropenia, ALT increased, nausea and vomiting, and 27 (16%) patients on chemotherapy, the most common of which were fatigue and dizziness. Dose reductions due to adverse events occurred in 28 (16%) patients on XALKORI, the most common of which were ALT increased, electrocardiogram QT prolonged and neutropenia, and 25 (15%) patients on chemotherapy, the most common of which were neutropenia, fatigue and mucosal inflammation. Adverse events resulting in permanent discontinuation occurred in 17% of patients on XALKORI, the most common of which were disease progression and interstitial lung disease, and 13% of patients on chemotherapy, the most common of which was febrile neutropenia.

Table 1 compares adverse drug reactions, regardless of causality, experienced by patients in the XALKORI and chemotherapy arms of Study A8081007.

Table 1. Adverse Drug Reactions Reported in Patients Who Received XALKORI or Chemotherapy in Randomized Phase 3 Study A8081007

Adverse Reaction[b], n (%)	XALKORI (N=172)		Chemotherapy (N=171)	
	All Grades	Grade ¾	All Grades	Grade ¾
Blood and Lymphatic System Disorders				
Neutropenia[a]	47 (27)	23 (13)	39 (23)	33 (19)
Leukopenia	15 (9)	3 (2)	9 (5)	4 (2)
Cardiac Disorders				
Electrocardiogram QT prolonged	8 (5)	6 (3)	0 (0)	0 (0)
Bradycardia[a]	8 (5)	0 (0)	0 (0)	0 (0)
Syncope	5 (3)	5 (3)	0 (0)	0 (0)
Eye Disorders				
Vision Disorder[a]	103 (60)	0 (0)	16 (9)	0 (0)
Gastrointestinal Disorders				
Vomiting	80 (47)	2 (1)	30 (18)	0 (0)
Nausea	95 (55)	0 (0)	64 (37)	1(1)
Diarrhea	103 (60)	0 (0)	33 (19)	1 (1)
Constipation	73 (42)	4 (2)	39 (22)	0 (0)
Dyspepsia	14 (8)	0 (0)	6 (3)	0 (0)
General Disorders and Administration Site Conditions				
Fatigue	46 (27)	4 (2)	57 (33)	7 (4)
Edema[a]	54 (31)	0 (0)	27 (16)	0 (0)
Hepatobiliary Disorders				
Elevated Transaminases[a]	66 (38)	27 (16)	25 (15)	4 (2)
Blood alkaline phosphatase increased	13 (8)	1 (1)	6 (3)	0 (0)
Hepatic failure	1 (1)	1 (1)	0 (0)	0 (0)
Infections and Infestations				
Upper Respiratory Infection[a]	44 (26)	0 (0)	22 (13)	1 (1)
Metabolism and Nutritional Disorders				
Decreased appetite	47 (27)	4 (2)	45 (26)	3 (2)
Hypokalemia	9 (5)	6 (4)	4 (2)	0 (0)

Nervous System Disorder				
Neuropathy[a]	33 (19)	1 (1)	29 (17)	2 (1)
Dizziness[a]	37 (22)	1 (1)	14 (8)	0 (0)
Dysgeusia	44 (26)	0 (0)	16 (9)	0 (0)
Syncope	5 (3)	5 (3)	0 (0)	0(0)
Renal and Urinary Disorders				
Renal Cyst[a]	7 (4)	0 (0)	0 (0)	0 (0)
Respiratory, Thoracic and Mediastinal Disorders				
Interstitial Lung Disease[a]	7 (4)	1 (1)	1 (1)	0 (0)
Pulmonary Embolism[a]	10 (6)	9 (5)	4 (2)	3 (2)
Skin and Subcutaneous Tissue Disorders				
Rash	15 (9)	0 (0)	29 (17)	0 (0)

a. Includes cases reported within the clustered terms: Neutropenia (Febrile neutropenia, Neutropenia, Neutrophil count decreased), Neuropathy (Dysaesthesia, Gait disturbance, Hypoaesthesia, Muscular weakness, Neuralgia, Neuropathy peripheral, Paraesthesia, Peripheral sensory neuropathy, Polyneuropathy, Skin burning sensation), Dizziness (Balance disorder, Dizziness, Dizziness postural), Vision Disorder (Diplopia, Photophobia, Photopsia, Vision blurred, Visual acuity reduced, Visual impairment, Vitreous floaters), Bradycardia (Bradycardia, Sinus bradycardia), Interstitial Lung Disease (Acute respiratory distress syndrome, Interstitial lung disease, Pneumonitis), Elevated Transaminases (Alanine aminotransferase increased, Aspartate aminotransferase increased, Gamma-glutamyltransferase increased, Hepatic function abnormal, Transaminases increased), Renal Cyst (Renal cyst), Edema (Face oedema, Generalised oedema, Local swelling, Localised oedema, Oedema, Oedema peripheral, Periorbital oedema). Pulmonary embolism (Pulmonary artery thrombosis, Pulmonary embolism), Upper respiratory infection (Laryngitis, Nasopharyngitis, Pharyngitis, Rhinitis, Upper respiratory tract infection).
b. Adverse reaction incidences were not adjusted for the difference in duration of study treatment; median was 7.1 months for patients who received XALKORI and 2.8 months for patients who received chemotherapy.

The following treatment-related Serious Adverse Events (SAEs) were reported in XALKORI clinical studies:

Common Clinical Trial Treatment-Related SAEs (≥1% to <10%):

Vomiting, Pneumonia, Alanine aminotransferase increased, Aspartate aminotransferase increased, Electrocardiogram QT prolonged, Interstitial lung disease

Uncommon Clinical Trial Treatment-Related SAEs (≥0.1% to <1%):

Febrile neutropenia, Neutropenia, Arrhythmia, Cardiac arrest, Abdominal pain upper, Diarrhoea, Nausea, Fatigue, Pyrexia, hepatic failure, Hepatitis, Decreased appetite, Hypokalaemia, Syncope, Renal cyst, Acute respiratory failure, Pneumonitis, Pulmonary artery thrombosis, Pulmonary thrombosis, Drug eruption, Pelvis venous thrombosis

Single-Arm Studies in ALK-Positive Advanced NSCLC (Studies A8081001 and A8081005)

The safety analysis population in Study A8081005 included 934 patients who received XALKORI. The median duration of treatment was 23 weeks. Dosing interruptions and dose

reductions due to treatment-related adverse events occurred in 212 (23%) patients and 116 (12%) of patients, respectively, in Study A8081005. The rate of treatment-related adverse events resulting in permanent discontinuation was 5% in Study A8081005. The most common treatment-related adverse events (≥10%) in Study A8081005 were vision disorder, diarrhea, nausea, vomiting, constipation, edema, elevated transaminases, dysgeusia, decreased appetite, fatigue, dizziness, neutropenia, and neuropathy. The most common Grade 3 or 4 treatment-related adverse events (≥2%) in Study A8081005 were neutropenia, elevated transaminases and fatigue. The potentially serious adverse reactions of pneumonitis and QT interval prolongation are discussed in WARNINGS AND PRECAUTIONS.

The safety analysis population in Study A8081001 included 119 patients who received XALKORI. The median duration of treatment was 32 weeks. Dosing interruptions and dose reductions due to adverse events occurred in 33% of patients, most common of which were ALT increased, pyrexia and pneumonia, and 6% of patients, most common of which was ALT increased, respectively. The rate of adverse events resulting in permanent discontinuation was 6%, most common of which was pneumonitis. The most common treatment-related adverse reactions (≥10 %) are consistent with Studies A8081007 and A8081005, and were vision disorder, nausea, diarrhea, vomiting, edema, constipation, dizziness, fatigue, ALT increased, and neuropathy.

Six unexplained deaths (<1%) occurred during treatment with XALKORI in these studies.

Table 2 Adverse Drug Reactions Reported at a Very Common Frequency (≥10%) in Patients with ALK-Positive Advanced NSCLC on Studies A8081001[a] and A8081005[a] – in at least 1 study

Adverse Reaction, n (%)	Study A8081001 RP2D (N=119)		Study A8081005 (N=934)	
	All Grades	Grade ¾	All Grades	Grade ¾
Blood and Lymphatic System Disorders				
Neutropenia[b]	6 (5)	4 (3)	125 (13)	72 (8)
Eye Disorders				
Vision Disorder[b]	75 (63)	0 (0)	513 (55)	4 (<1)
Gastrointestinal Disorders				
Nausea	59 (50)	1 (1)	476 (51)	18 (2)
Diarrhea	57 (48)	1 (1)	432 (46)	11 (1)
Vomiting	48 (40)	1 (1)	433 (46)	12 (1)
Constipation	45 (38)	1 (1)	356 (38)	4 (<1)
Dyspepsia	14 (12)	0 (0)	55 (6)	0 (0)
General Disorders and Administration Site Conditions				
Edema[b]	43 (36)	1 (1)	360 (39)	13 (1)
Fatigue	30 (25)	3 (3)	239 (26)	28 (3)
Investigations				
Elevated Transminases[b]	24 (20)	10 (8)	221 (24)	65 (7)
Metabolism and Nutritional Disorders				
Decreased Appetite	28 (24)	1 (1)	228 (24)	7 (<1)

Nervous System Disorder				
Dizziness[b]	35 (29%)	0 (0)	173 (19)	4 (<1)
Neuropathy[b]	24 (20)	1 (<1)	178 (19)	9 (1)
Dysgeusia	10 (8)	0 (0)	178 (19)	0 (0)
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnoea[bc]	22 (18)	6 (5)	184 (20) [c]	43 (5)
Cough[b]	16 (13)	1 (1)	194 (21)	3 (<1)
Skin and Subcutaneous Tissue Disorders				
Rash	21 (18)	0 (0)	89 (10)	1 (<1)

RP2D: Recommended Phase 2 Dose

a. Study A8081001 used NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, and Study A8081005 used NCI CTCAE version 4.0

b. Includes cases reported as clustered terms: cough (cough, productive cough), dizziness (balance disorder, dizziness, dizziness exertional, dizziness postural, presyncope), dyspnoea (dyspnoea, dyspnoea at rest, dyspnoea exertional, dyspnoea paroxysmal nocturnal, nocturnal dyspnoea, orthopnoea), edema (edema, edema peripheral, face oedema, generalized oedema, local swelling, localized oedema, oedema (edema), oedema peripheral (edema peripheral), periorbital oedema), elevated transaminases (alanine aminotransferase, alanine aminotransferase abnormal, alanine aminotransferase increased, aspartate aminotransferase, aspartate aminotransferase abnormal, aspartate aminotransferase increased, gamma-glutamyltransferase abnormal, gamma-glutamyltransferase increased, hepatic enzyme abnormal, hepatic enzyme increased, hepatic function abnormal, hypertransaminasaemia, liver function test abnormal, transaminases, transaminases abnormal, transaminases increased), neuropathy (acute polyneuropathy, amyotrophy, areflexia, autoimmune neuropathy, autonomic failure syndrome, autonomic neuropathy, axonal neuropathy, biopsy peripheral nerve abnormal, burning feet syndrome, burning sensation, decreased vibratory sense, demyelinating polyneuropathy, dysaesthesia, electromyogram abnormal, formication, gait disturbance, genital hypoaesthesia, Guillain-Barre syndrome, hyperaesthesia, hypoaesthesia, hyporeflexia, hypotonia, ischaemic neuropathy, loss of proprioception, Miller Fisher syndrome, mononeuritis, mononeuropathy, mononeuropathy multiplex, motor dysfunction, multifocal motor neuropathy, muscle atrophy, muscular weakness, myelopathy, nerve conduction studies abnormal, nerve degeneration, neuralgia, neuritis, neuromuscular toxicity, neuromyopathy, neuropathy peripheral, neuropathy vitamin B6 deficiency, neurotoxicity, paraesthesia, peripheral motor neuropathy, peripheral nerve lesion, peripheral nerve palsy, peripheral nervous system function test abnormal, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, peroneal muscular atrophy, peroneal nerve palsy, phrenic nerve paralysis, polyneuropathy, polyneuropathy chronic, polyneuropathy idiopathic progressive, radiation neuropathy, sensorimotor disorder, sensory disturbance, sensory loss, skin burning sensation, temperature perception test decreased, Tinel's sign, toxic neuropathy, ulnar neuritis), neutropenia (febrile neutropenia, neutropenia, neutrophil count decreased), and vision disorder (diplopia, halo vision, photophobia, photopsia, vision blurred, visual field defect, visual impairment, vitreous floaters, visual acuity reduced, visual brightness).

c. Includes 6 Grade 5 events

Table 3 Adverse Drug Reactions Reported at a Common Frequency (≥1% to <10%) in Patients with ALK-Positive Advanced NSCLC on Studies A8081001[a] and A8081005[a] - in at least 1 study

Adverse Reaction, n (%)	Study A8081001 RP2D (N=119)		Study A8081005 (N=934)	
	All Grades	Grade ¾	All Grades	Grade ¾
Blood and Lymphatic System Disorders				
Leukopenia	6 (5)	0 (0)	58 (6)	14 (2)
Lymphopenia	6 (5)	3(3)	34 (4)	25 (3)
Cardiac Disorders				
Bradycardia[b]	8 (7)	0 (0)	57 (6)	2(<1)
Investigations				
Electrocardiogram QT Prolonged	1 (1)	0 (0)	25 (3)	11 (1)
Renal and Urinary Disorders				
Renal Cyst[b]	0 (0)	0 (0)	12 (1)	1 (<1)
Respiratory, Thoracic and Mediastinal Disorders				
Interstitial Lung Disease[bc]	3 (3)	3(3)	22 (2)[c]	8 (1)
Vascular Disorders				
Hypotension	6 (5)	0 (0)	36 (4)	6 (<1)

RP2D: Recommended Phase 2 Dose

a. Study A8081001 used NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, and Study A8081005 used NCI CTCAE version 4.0

b. Includes cases reported as clustered terms: bradycardia (bradyarrhythmia, bradycardia, heart rate decreased, sinus bradycardia, sinus arrest), interstitial lung disease (acute interstitial pneumonitis, acute lung injury, acute respiratory distress syndrome, alveolitis, alveolitis allergic, alveolitis fibrosing, alveolitis necrotising, diffuse alveolar damage, eosinophilic pneumonia, eosinophilic pneumonia acute, interstitial lung disease, pneumonitis, pulmonary toxicity), renal cyst (renal abscess, renal cyst, renal cyst excision, renal cyst haemorrhage, renal cyst infection, renal cyst ruptured)

c. Includes 1 Grade 5 event

The following treatment-related Serious Adverse Events (SAEs) were reported in XALKORI clinical studies:

Common Clinical Trial Treatment-Related SAEs (≥1% to <10%)

The following treatment-related SAE was reported with XALKORI treatment at a common frequency (≥1% to <10%): pneumonitis (2%).

Uncommon Clinical Trial Treatment-Related SAEs (≥0.1% to <1%)

The following treatment-related SAEs were reported with XALKORI treatment at an uncommon frequency (≥0.1% to <1%): alanine aminotransferase increased (0.4%), constipation (0.4%), death (0.4%), dyspnoea (0.4%), febrile neutropenia (0.4%), haematoma (0.4%), hepatic enzyme increased (0.4%), hypokalaemia (0.4%), hyponatraemia (0.4%), infection (0.4%), liver function test abnormality (0.4%), oedema peripheral (0.4%), oesophageal ulcer (0.4%), pneumonia (0.4%), renal abscess (0.4%), and supraventricular tachycardia (0.4%).

There were no clinical trial SAEs that occurred at a rare frequency (≤0.1%).

Electrocardiography and Haemodynamics

ECG evaluations were performed in all patients who received XALKORI 250 mg twice daily. Serial ECGs in triplicate were collected following a single dose and at steady state to evaluate the effect of XALKORI on QT intervals. Crizotinib 250 mg twice daily was associated with a statistically significant decrease in heart rate during steady-state treatment (see ADVERSE REACTIONS). At 6 hours post-dosing on Day 22 of treatment, heart rate was decreased by mean 15.9 beats per minute (90% CI: -17.9, -13.8) in 105 ALK-positive NSCLC patients in Study A8081005.

XALKORI 250 mg twice daily was also associated with a statistically significant prolongation of the QTcF interval (Fridericia-corrected QT interval) during steady-state treatment. At 6 hours post-dosing on Day 22 of treatment, the QTcF interval was prolonged by mean increase from baseline of 10.3 msec (90% CI: 7.3, 13.3). Across Studies A8081001, A8081005, and A8081007, 34 patients (3%) had an adverse reaction of electrocardiogram QT prolonged. In addition, across Studies A8081001, A8081005, and A8081007, 16 of 1167 patients (1.4%) were found to have QTcF ≥500 msec and 51 of 1136 patients (4.5%) had an increase from baseline QTcF >60 msec by automated machine-read evaluation of ECG.

An ECG substudy from Studies A8081005 and A8081007 using blinded manual ECG measurements was conducted in 52 ALK-positive NSCLC patients who received crizotinib 250 mg twice daily. A total of 11 (21.2%) patients and 1 (1.9%) patient had a maximum increase from baseline in QTcF of ≥30 msec to < 60 msec and ≥ 60 msec, respectively, and no patients had a maximum QTcF ≥ 480 msec in this analysis. The central tendency analysis indicated that the largest mean change from baseline in QTcF was 12.3 msec (90% CI: 5.1, 19.5) (least squares [LS] mean from Analysis of Variance [ANOVA]) and occurred at 6 hours post-dose on Cycle 2 Day 1 (steady state). All upper limits of the 90% CI for the LS mean change from baseline in QTcF at all Cycle 2 Day 1 time points were <20 msec. HR decreased with a maximum reduction of 17.8 (range: -51 to +9) beats per minutes after 8 hours on Cycle 2 Day 1 (last ECG collecting time point). Bradycardia was reported in 6 (9.2%) patients.

Pharmacokinetic/pharmacodynamic modeling indicated a concentration-dependent increase in QTcF and decrease in HR (see WARNINGS AND PRECAUTIONS, Cardiovascular & Monitoring and Laboratory Tests; DRUG INTERACTIONS; DOSAGE AND ADMINISTRATION).

Ophthalmologic

Vision disorder, most commonly visual impairment, photopsia, vision blurred, and vitreous floaters, was experienced by 103 (60%) patients in Study A8081007, 75 (63%) patients in Study A8081001, and 513 (55%) patients in Study A8081005. Greater than 95% of these patients had events that were mild in severity with median time to onset of 5 days and 7 days in Studies A8081007, A8081001 and A8081005, respectively. None of the patients in Studies A8081007, A8081001 and A8081005 required dosing interruption, dose reduction, or permanent discontinuation from study treatment for vision disorder, except 1 patient from Study A8081001

and 4 patients from Study A8081005 who had temporary treatment discontinuation and 1 patient from Study A8081005 and 1 patient from Study A8081007 who had dose reduction for vision disorder. Ophthalmological evaluation should be considered if vision disorder persists or worsens in severity. Caution should be exercised when driving or operating machinery by patients who experience vision disorder (see Non Clinical Toxicology section).

Gastrointestinal

Nausea (51% [59/119 (50%) in Study A8081001, 476/934 (51%) in Study A8081005, and 94/172 (55%) in Study A8081007]), diarrhea (48% [57/119 (48%) in Study A8081001, 432/934 (46%) in Study A8081005, and 103/172 (60%) in Study A8081007]), vomiting (46% [48/119 (40%) in Study A8081001, 433/934 (46%) in Study A8081005, and 80/172 (47%) in Study A8081007]), and constipation (39% [45/119 (38%) in Study A8081001, 356/934 (38%) in Study A8081005, and 73/172 (42%) in Study A8081007]) were the most commonly reported gastrointestinal events (see ADVERSE REACTIONS). Median times to onset for nausea and vomiting was 2 to 3 days across Studies A8081007, A8081001, and A8081005. Most events were mild to moderate in severity, and declined in frequency after 3 to 4 weeks of treatment. Supportive care may include the use of antiemetic medications. In clinical trials, the most commonly used antiemetic medications were ondansetron and prochlorperazine. Diarrhea and constipation were primarily mild to moderate in severity. Supportive care for diarrhea and constipation may include the use of standard antidiarrheal and laxative medications, respectively.

Neurologic

Neuropathy (motor and sensory, see Table 1), was experienced by 33 (19%) of patients in randomized Phase 3 Study A8081007, 24 (20%) patients in Study A8081001 and 178 (19%) patients in Study A8081005, and was mainly Grade 1 in severity. Dizziness (20%) and dysgeusia (19%) were also commonly reported in these studies, and were primarily Grade 1 in severity. CNS haemorrhage has been reported in 2 (<1%) patients treated with crizotinib, both of whom were pediatric patients with previously treated primary intracranial tumors, 1 of whom had a fatal outcome (see Non Clinical Secondary Pharmacodynamics section).

Abnormal Hematologic and Clinical Chemistry Findings

Table 4a. Summary of Treatment-Emergent Laboratory Abnormalities with Shift to Grade 3 or 4 Incidence of ≥4% in XALKORI-Treated Patients – Study A8081007

Laboratory Abnormality	Crizotinib		Chemotherapy	
	Shift to Any Grade	Shift to Grade ¾	Shift to Any Grade	Shift to Grade ¾
Hematology				
Neutropenia	49%	12%	28%	12%
Lymphopenia	51%	9%	60%	25%
Chemistry				
ALT elevation	76%	17%	38%	4%
AST elevation	61%	9%	33%	0%
Hypokalemia	18%	4%	10%	1%
Hypophosphatemia	28%	5%	25%	6%

Table 4b. Summary of Treatment-Emergent Laboratory Abnormalities with Shift to Grade 3 or 4 Incidence of ≥4% in XALKORI-Treated Patients – Study A8081005

Laboratory Abnormality	Shift to Any Grade	Shift to Grade ¾
Hematology		
Neutropenia	38%	8%
Lymphopenia	48%	15%
Chemistry		
ALT elevation	67%	8%
Hypophosphatemia	30%	8%
Hyponatremia	18%	5%

Table 4c. Summary of Treatment-Emergent Laboratory Abnormalities with Shift to Grade 3 or 4 Incidence of ≥4% in XALKORI-Treated Patients – Study A8081001

Laboratory Abnormality	Shift to Any Grade	Shift to Grade ¾
Hematology		
Lymphopenia	35%	11%
Chemistry		
ALT elevation	65%	5%
Hypophosphatemia	42%	5%
Hyponatremia	21%	5%
Hyperglycemia	44%	4%

Hepatic Laboratory Abnormalities

In Study A8081007, shifts to Grade 3 or 4 increases in ALT, AST, alkaline phosphatase, and total bilirubin were observed in patients at frequencies of 17%, 9%, 2%, and 1%, respectively. In Study A8081001, shifts to Grade 3 or 4 increases in ALT, AST, alkaline phosphatase, and total bilirubin were observed in patients at frequencies of 5%, 3%, 0%, and 0%, respectively. In Study A8081005, shifts to Grade 3 or 4 increases in ALT, AST, alkaline phosphatase, and total bilirubin were observed in patients at frequencies of 8%, 4%, 2%, and <1%, respectively. Patients should be monitored for hepatotoxicity and managed as recommended in WARNINGS AND PRECAUTIONS section.

Drug-induced hepatotoxicity, including hepatic failure, with fatal outcome has occurred in 1% of patients treated with crizotinib. Concurrent elevations in ALT >3 x ULN and total bilirubin >2 x ULN without elevated alkaline phosphatase (Hy's Law) have been observed in <1% patients in clinical trials. Shifts to Grade 3 or 4 ALT elevation was observed in 17% of patients in Study A8081007, 4% of patients in Study A8081001 and 8% of patients in Study A8081005. These laboratory findings were generally asymptomatic, and reversible upon dosing interruption. Patients usually resumed treatment at a lower dose without recurrence; however, 2 patients from Study A8081007 (1%), 1 patient from Study A8081001 (<1%) and 5 patients from Study A8081005 (<1%) required permanent discontinuation from treatment. Concurrent elevations in ALT >3 x ULN and total bilirubin >2 x ULN without elevated alkaline phosphatase were detected in <1% patients in clinical trials. Liver function tests including ALT and total bilirubin should be monitored every 2 weeks during the first 2 months of treatment, then once a month and as clinically indicated, with more frequent repeat testing for Grades 2, 3 or 4 elevation. In patients who develop transaminase elevations, see Dose Modification section under DOSAGE AND ADMINISTRATION.

Hematologic Effects

In Study A8081007, shifts to Grade 3 or 4 decreases in platelets were observed in patients at a frequency of <1%, and shifts to Grade 3 or 4 decreases in leukocytes, lymphocytes, and neutrophils were observed at frequencies of 5%, 9%, and 13%, respectively. In Study A8081001, shifts to Grade 3 or 4 decreases in neutrophils, leukocytes, and platelets were each observed in patients at frequencies of <4%, and shifts to Grade 3 or 4 decreases in lymphocytes were observed at a frequency of 12%. In Study A8081005, shifts to Grade 3 or 4 decreases in leukocytes and platelets were each observed in patients at frequencies of ≤3%, and shifts to Grade 3 or 4 decreases in neutrophils and lymphocytes were observed at frequencies of 8% and 15%, respectively. Complete blood counts, including differential white blood cell counts, should be monitored as clinically indicated, with more frequent repeat testing if Grade 3 or 4 abnormalities are observed, or if fever or infection occurs. In patients who develop hematologic laboratory abnormalities, see Dose Modification section under DOSAGE AND ADMINISTRATION.

DRUG INTERACTIONS

Overview

Crizotinib is a substrate and inhibitor of CYP3A and an inhibitor of CYP2B6. It is also a substrate and an inhibitor of P-glycoprotein (P-gp). The aqueous solubility of crizotinib is pH-dependent. Drug interactions were observed when crizotinib was co-administered with a strong CYP3A inhibitor, a strong CYP3A inducer, and a substrate of CYP3A. Drug interactions may occur when crizotinib is co-administered with other QTc-prolonging and heart rate-lowering drugs. The related findings and precautions are discussed further below.

Drug-Drug Interactions

Drugs That May Increase Crizotinib Plasma Concentrations

CYP3A Inhibitors

Crizotinib is predominantly metabolized by CYP3A. Co-administration of crizotinib with CYP3A inhibitors may increase crizotinib plasma concentrations. Co-administration of a single 150 mg oral dose of crizotinib in the presence of ketoconazole (200 mg twice daily), a strong CYP3A4 inhibitor, resulted in increases in crizotinib systemic exposure, with crizotinib AUC_{inf} and C_{max} values that were approximately 3.2-fold and 1.4-fold, respectively, those seen when crizotinib was administered alone. However, the magnitude of effect of CYP3A inhibitors on steady state crizotinib exposure has not been established. The concomitant use of strong CYP3A inhibitors, including but not limited to, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, and voriconazole, should be avoided (see DOSAGE AND ADMINISTRATION section). Caution should be exercised when moderate CYP3A inhibitors are co-administered.

Drugs That May Decrease Crizotinib Plasma Concentrations

CYP3A Inducers

Co-administration of crizotinib with CYP3A inducers may decrease crizotinib plasma concentrations. Co-administration of a single 250 mg crizotinib dose with rifampin (600 mg once daily), a strong CYP3A inducer, resulted in 82% and 69% decreases in crizotinib AUC_{inf} and C_{max}, respectively, compared to when crizotinib was given alone. However, the effect of CYP3A inducers on steady state crizotinib exposure has not been established. The concurrent use of strong CYP3A inducers, including but not limited to, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort, should be avoided (see DOSAGE AND ADMINISTRATION section).

Agents That Increase Gastric pH

The aqueous solubility of crizotinib is pH-dependent, with high (less acidic) pH resulting in lower solubility. The ratio of adjusted geometric means (90% CI) of crizotinib total exposure

(AUC_{inf}) was 89.81% (79.05%, 102.03%), following administration of crizotinib 250 mg relative to crizotinib 250 mg and esomeprazole (40 mg QD × 5 days). Based on the extent of the change in total exposure, starting dose adjustment is not required when crizotinib is co-administered with agents that increase gastric pH (such as proton pump inhibitors, H_2 blockers, or antacids).

Drugs Whose Plasma Concentrations May Be Altered by Crizotinib

CYP3A Substrates

Crizotinib has been identified as an inhibitor of CYP3A both *in vitro* and *in vivo*. Crizotinib may increase plasma concentrations of co-administered CYP3A substrates. Following 28 days of crizotinib dosing at 250 mg taken twice daily in cancer patients, the oral midazolam AUC was 3.65-fold (90% CI: 2.63-5.07) those seen when midazolam was administered alone, suggesting that crizotinib is a moderate inhibitor of CYP3A.

Caution should be exercised in administering crizotinib in combination with drugs that are predominantly metabolized by CYP3A, particularly those CYP3A substrates that have narrow therapeutic indices, including but not limited to alfentanil, cyclosporine, fentanyl, quinidine, sirolimus, and tacrolimus. Co-administration of crizotinib should be avoided with CYP3A substrates that have narrow therapeutic indices and are associated with life-threatening arrhythmias, including but not limited to dihydroergotamine, ergotamine, and pimozide.

CYP2B6 Substrates

Crizotinib is an inhibitor of CYP2B6 *in vitro*. Therefore, crizotinib may have the potential to increase plasma concentrations of co-administered drugs that are predominantly metabolized by CYP2B6.

Other CYP Substrates

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

In vitro studies in human hepatocytes indicated that clinical drug-drug interactions are unlikely to occur as a result of crizotinib-mediated induction of the metabolism of drugs that are substrates for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A (see DETAILED PHARMACOLOGY section).

Co-administration with UGT Substrates

Crizotinib is identified as a competitive inhibitor of UGT enzyme isoforms UGT 1A1 and UGT2B7 *in vitro* with IC50 values IC50 5.3 μM and 6.9 μM, respectively. Therefore, crizotinib may have the potential to increase plasma concentrations of co-administered drugs that are metabolized predominantly by UGT1A1 (e.g., raltegravir, irinotecan) or UGT2B7 (e.g., morphine, naloxone) (see DETAILED PHARMACOLOGY).

P-gp Substrates

Crizotinib is an inhibitor of P-gp *in vitro*. Therefore, crizotinib may have the potential to increase plasma concentrations of co-administered drugs that are substrates of P-gp.

OCT Substrates

Crizotinib is an inhibitor of OCT1 (IC50 = 2.4μM) and OCT2 (IC50 = 0.22μM) *in vitro*. Therefore, crizotinib may have the potential to increase plasma concentrations of co-administered drugs that are substrates of OCT1 or OCT2 (see DETAILED PHARMACOLOGY).

Heart Rate-Lowering Drugs

Bradycardia has been reported in patients treated with XALKORI (see WARNINGS AND PRECAUTIONS, Cardiovascular & Monitoring and Laboratory Tests; ADVERSE REACTIONS, Electrocardiography and Haemodynamics). Avoid using crizotinib in combination with other bradycardic agents (e.g., beta-blockers, non-dihydropyridine calcium channel blockers, cholinesterase inhibitors, and sphingosine-1 phosphate receptor modulators) (including but not limited to atenolol, verapamil, diltiazem, clonidine, digoxin to the extent possible, due to the increased risk of symptomatic bradycardia (syncope, dizziness, hypotension).

QT Interval-Prolonging Drugs

The concomitant use of XALKORI with QT interval-prolonging drugs should be avoided to the extent possible (see WARNINGS AND PRECAUTIONS, Cardiovascular & Monitoring and Laboratory Tests; ADVERSE REACTIONS, Electrocardiography and Haemodynamics). Drugs that have been associated with QT interval prolongation and/or Torsade de Pointes include, but are not limited to, the examples in the following list. Chemical/pharmacological classes are listed if some, although not necessarily all, class members have been implicated in QT/QTc interval prolongation and/or Torsade de Pointes:

- Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide)
- Class III antiarrhythmics (e.g., amiodarone, sotalol, ibutilide, dronedarone)
- Class 1C antiarrhythmics (e.g., flecainide, propafenone)
- antipsychotics (e.g., chlorpromazine, pimozide, haloperidol, droperidol, ziprasidone)
- antidepressants (e.g., fluoxetine, citalopram, venlafaxine, tricyclic/tetracyclic antidepressants [e.g., amitriptyline, imipramine, maprotiline])
- opioids (e.g., methadone)
- macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin, telithromycin, tacrolimus)
- quinolone antibiotics (e.g., moxifloxacin, levofloxacin, ciprofloxacin)
- pentamidine
- antimalarials (e.g., quinine, chloroquine)

- azole antifungals (e.g., ketoconazole, fluconazole, voriconazole)
- domperidone
- 5-hydroxytryptamine $(5\text{-HT})_3$ receptor antagonists (e.g., dolasetron, ondansetron)
- tyrosine kinase inhibitors (e.g., sunitinib, nilotinib, lapatinib, vandetanib)
- histone deacetylase inhibitors (e.g., vorinostat)
- beta-2 adrenoceptor agonists (e.g., salmeterol, formoterol)

Drugs that Affect Electrolytes

The use of XALKORI with drugs that can disrupt electrolyte levels should be avoided to the extent possible. Drugs that can disrupt electrolyte levels include, but are not limited to, the following:

- loop, thiazide, and related diuretics
- laxatives and enemas
- amphotericin B
- high-dose corticosteroids

The above list of potentially interacting drugs is not comprehensive. Current information sources should be consulted for newly approved drugs that decrease heart rate, prolong the QT/QTc interval, or decrease electrolytes, as well as for older drugs for which these effects have recently been established.

Drug-Food Interactions

Grapefruit has CYP3A4 inhibitory activity. Therefore, ingestion of grapefruit while on XALKORI (crizotinib) therapy may increase crizotinib plasma concentrations. Concomitant administration of XALKORI with grapefruit, grapefruit juice, products containing grapefruit extract, star fruit, pomegranate, Seville oranges, and other similar fruits that are known to inhibit CYP3A4 should be avoided.

Drug-Herb Interactions

St. John's wort is a strong CYP3A4 inducer. Co-administration with XALKORI may decrease crizotinib plasma concentrations. Patients receiving XALKORI should not take St. John's wort concomitantly.

Drug-Lifestyle Interactions

Vision disorder, that was considered related to treatment with XALKORI, most commonly visual impairment, photopsia, vision blurred, and vitreous floaters, was experienced by 101 (59%) patients in Study A8081007, 74 (62%) patients in Study A8081001, and 496 (53%) patients in Study A8081005. Caution should be exercised when driving or operating machinery by patients who experience vision disorder.

NOC/c

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

The recommended dose schedule of XALKORI (crizotinib) is 250 mg taken orally twice daily

with or without food. Treatment should be continued as long as the patient is deriving clinical benefit from therapy. Capsules should be swallowed whole.

The concurrent use of strong CYP3A inhibitors such as ketoconazole should be avoided (see DRUG INTERACTIONS and CLINICAL PHARMACOLOGY sections).

The concurrent use of strong CYP3A inducers such as rifampin should be avoided (see DRUG INTERACTIONS and CLINICAL PHARMACOLOGY sections).

Missed Dose

If a dose of XALKORI is missed, then it should be taken as soon as possible. If it is less than 6 hours until the next dose, then the patient should not take the missed dose. Patients should not take 2 doses at the same time to make up for a missed dose.

Dose Modification

Dose reduction and/or treatment interruption may be required based on individual safety and tolerability. Based on clinical trial dose reduction recommendations, if dose reduction is necessary, then the dose of XALKORI may be reduced to 200 mg taken orally twice daily. If further dose reduction is necessary, the dose may be modified to 250 mg taken orally once daily based on individual safety and tolerability. Dose modification guidelines for hematologic and non-hematologic toxicities are provided in Tables 5 and 6.

Table 5. XALKORI Dose Modification – Hematologic Toxicities[a]

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

a. Except lymphopenia (unless associated with clinical events, e.g., opportunistic infections)
b. NCI Common Terminology Criteria for Adverse Events
c. In case of recurrence, withhold until recovery to Grade ≤2 or baseline, then resume at 250 mg taken orally once daily. Permanently discontinue in case of further Grade 4 recurrence.

Table 6. XALKORI Dose Modification – Non-Hematologic Toxicities

CTCAE[a] Grade	XALKORI Dosing
Grade 3 or 4 ALT or AST elevation with Grade ≤1 total bilirubin	Withhold until recovery to Grade ≤1 or baseline, then resume at 200 mg twice daily[b]
Grade 2, 3 or 4 ALT or AST elevation with concurrent Grade 2, 3 or 4 total bilirubin elevation (in the absence of cholestasis or hemolysis)	Permanently discontinue
Any grade interstitial lung disease/pneumonitis[c]	Permanently discontinue
Grade 3 QTc prolongation (≥500 msec)	Withhold until recovery to Grade <1 (≤ 470 msec), then resume at 200 mg twice daily[b]
Grade 4 QTc prolongation (≥500 msec [or >60 msec change from baseline] and Torsade de Pointes or polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmias)	Permanently discontinue
Grade 2, 3 Bradycardia[d] (symptomatic, may be severe and medically significant, medical intervention indicated)	Withhold until recovery to Grade ≤ 1 or to heart rate of 60 bpm or above Evaluate concomitant medications known to cause bradycardia, as well as anti-hypertensive medications If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at previous dose upon recovery to Grade ≤ 1 or to 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 Grade ≤ 1 or to heart rate of 60 bpm or above
Grade 4 Bradycardia[d,e] (life-threatening consequences, urgent intervention indicated)	Permanently discontinue if no contributing concomitant medication is identified If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at 250 mg once daily upon recovery to Grade ≤ 1 or to heart rate of 60 bpm or above, with frequent monitoring

a. NCI Common Terminology Criteria for Adverse Events
b. In case of recurrence, withhold until recovery to Grade <1 or baseline, then resume at 250 mg taken orally once daily. Permanently discontinue in case of further Grade 3 or 4 recurrence.
c. In the absence of NSCLC progression, other pulmonary disease, infection, or radiation effect
d. Heart rate less than 60 beats per minute (bpm).
e. Permanently discontinue for recurrence.

QT Interval Prolongation

In the event of a QTc of ≥500 msec (Grade 3), dosing with XALKORI should be withheld until recovery to Grade ≤1 (≤470 msec), then resumed at a reduced dose of 200 mg twice daily. Permanent discontinuation of XALKORI is recommended in the event of a Grade 4 QTc prolongation (≥500 msec [or >60 msec change from baseline] and Torsade de Pointes or polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmias). Machine-read QTc measurements may not be accurate. Consultation with a cardiologist should be considered when assessing the QTcF to ensure appropriate treatment decisions. Baseline ECG QTcF should be measured prior to initiating treatment with XALKORI and ECGs should be repeated periodically during treatment with XALKORI. Hypokalemia, hypomagnesemia, and hypocalcemia must be corrected prior to XALKORI administration. Serum levels of calcium, potassium, and magnesium should be monitored periodically during treatment, particularly in patients at risk for these electrolyte abnormalities (see WARNINGS AND PRECAUTIONS).

Special Populations

No dedicated studies with XALKORI in patients with impaired hepatic function have been carried out therefore there is no available data regarding recommendations for dose adjustment. Treatment with XALKORI should be used with caution in patients with hepatic impairment (see ADVERSE REACTIONS and ACTION AND CLINICAL PHARMACOLOGY Special Populations and Conditions, Hepatic Impairment).

The starting dose of XALKORI should be reduced by 50% (250 mg once daily) in patients with severe renal impairment (CLcr < 30 mL/min) not requiring peritoneal dialysis or hemodialysis. No starting dose adjustment is recommended in patients with mild or moderate renal impairment, although data are limited. Patients with mild or moderate renal impairment should be treated with caution (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Impairment).

No data are available for patients with severe renal impairment requiring peritoneal dialysis or hemodialysis (CLcr < 30 mL/min) (see Serious Warnings and Precautions, and ACTION AND CLINICAL PHARMACOLOGY).

OVERDOSAGE

The recommended 250 mg BID dosing regimen was the maximum tolerated dose for XALKORI determined in a Phase 1 dose-escalation study in patients with advanced solid tumors. Treatment of overdose with XALKORI should consist of symptomatic treatment and other supportive measures. There is no antidote for XALKORI.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

NOC/c ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Crizotinib is a selective small-molecule inhibitor of the Anaplastic Lymphoma Kinase (ALK) receptor tyrosine kinase (RTK) and its oncogenic variants (i.e., ALK fusion events and selected ALK mutations). Crizotinib is also an inhibitor of the Hepatocyte Growth Factor Receptor (HGFR, c-Met) RTK, ROS (ROS1, c-ros), and Recepteur d'Origine Nantais (RON) RTKs.

Pharmacodynamics

Crizotinib demonstrated concentration-dependent inhibition of the kinase activity of ALK, ROS1, and c-Met in biochemical assays and inhibited phosphorylation and kinase-dependent phenotypes in cell-based assays. Crizotinib demonstrated potent and selective growth inhibitory activity and induced apoptosis in tumor cell lines exhibiting ALK fusion events (EML4-ALK or NPM-ALK), ROS1 fusion events, or exhibiting amplification of the *ALK* or *MET* gene locus. Crizotinib demonstrated antitumor efficacy, including marked cytoreductive antitumor activity, in mice bearing tumor xenografts that expressed ALK and ROS1 fusion proteins. The antitumor efficacy of crizotinib was dose-dependent and correlated to pharmacodynamic inhibition of phosphorylation of ALK (EML4-ALK or NPM-ALK) and ROS1 (CD74-ROS1 or EZR-ROS1) fusion proteins in tumors *in vivo*.

Pharmacokinetics

Absorption: In patients, following a single oral administration in the fasted state, crizotinib was absorbed with a median time to achieve peak concentrations (T_{max}) of 4 hours (range: 2 to 9.33 hours) in patients (see Clinical Pharmacokinetics section under DETAILED PHARMACOLOGY). The systemic exposure (C_{max}, C_{trough} and AUC_{tau}) appears to be greater than dose-proportional within the dose range of 200-300 mg twice daily. With twice daily dosing, steady state was achieved within 15 days with a median accumulation ratio of 4.8 (range: 3 to 13), and remained stable. The mean absolute bioavailability of crizotinib was determined to be 43% (range: 32%-66%) following the administration of a single 250 mg oral dose. Following oral administration of a single dose of a 250 mg XALKORI capsule to healthy volunteers in the fasted state, the median T_{max} was 5 hours, and the geometric mean C_{max} and AUC of crizotinib were 135 ng/mL and 2887 ng.hr/mL, respectively.

A high-fat meal reduced crizotinib AUC_{inf} and C_{max} by approximately 14% when a 250 mg single dose was given to healthy volunteers. XALKORI can be administered with or without food (see DOSAGE AND ADMINISTRATION section).

Distribution: The geometric mean volume of distribution (Vss) of crizotinib was 1772 L following intravenous administration of a 50 mg dose, indicating extensive distribution into tissues from the plasma. In non-clinical studies, tissues with the highest crizotinib and related metabolite concentrations were liver, uveal tract, adrenal gland, small intestine, and pituitary gland.

Binding of crizotinib to human plasma proteins *in vitro* is 91% and appears to be independent of drug concentration. *In vitro* studies suggested that crizotinib is a substrate for P-glycoprotein (P-gp).

Metabolism: *In vitro* studies demonstrated that CYP3A4/5 were the major enzymes involved in the metabolic clearance of crizotinib. The primary metabolic pathways in humans were oxidation of the piperidine ring to crizotinib lactam and *O*-dealkylation, with subsequent Phase 2 conjugation of *O*-dealkylated metabolites.

Crizotinib lactam (M10, PF-06260182) is approximately 2.5- and 7.7-fold less potent than crizotinib in inhibiting ALK and c-Met tyrosine kinases, respectively, *in vitro*. The O-desalkyl crizotinib (M4, PF-03255243) and *O*-desalkyl crizotinib lactam (M2, PF-06268935) are inactive against ALK and c-Met.

In vitro studies in human microsomes demonstrated that crizotinib is a time-dependent inhibitor of CYP3A and CYP2B6.

Elimination: Following a single 250 mg oral dose, the terminal half-life ($t_{1/2}$) of crizotinib was 42 hours (% coefficient of variation [CV]: 21) in patients; the mean apparent clearance (CL/F) was 100 L/hr (%CV: 50). At steady state after 250 mg twice daily (Cycle 1 Day 15), the CL/F appeared to be lower (65 L/hr with % CVof 56). The reduced clearance at steady state may be due to autoinhibition of CYP3A by crizotinib following repeated dosing.

In a non-clinical study, delayed clearance of crizotinib was observed; tissues with the longest $t_{1/2}$ values (range: 576 to 118 hours) were eye, epididymis, testis, pigmented skin, kidney cortex, and brown fat.

Following the administration of a single 250 mg radiolabeled crizotinib dose to healthy subjects, 63% and 22% of the administered dose was recovered in feces and urine, respectively. Unchanged crizotinib represented approximately 53% and 2.3% of the administered dose in feces and urine, respectively.

Special Populations and Conditions

Hepatic Impairment: XALKORI has not been studied in patients with hepatic impairment. Clinical studies that were conducted excluded patients with ALT or AST >2.5 x upper limit of normal (ULN) or, if due to underlying malignancy, >5.0 x ULN, or with total bilirubin >1.5 x ULN. Therefore, treatment with XALKORI should be used with caution in patients with hepatic impairment (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Special Populations).

Renal Impairment: The exposure to crizotinib was evaluated in patients with mild (CLcr 60-89 mL/min, N=226) and moderate (CLcr 30-59 mL/min, N=73) renal impairment enrolled in Studies A8081001 and A8081005. An evaluation on the baseline renal function status measured by CLcr on observed crizotinib steady state trough concentrations ($C_{trough, ss}$) demonstrated that in Study A8081001, the adjusted geometric mean of plasma $C_{trough, ss}$ in mild ($C_{trough, ss}$ = 319 ng/mL, N=35) and moderate ($C_{trough, ss}$ = 338 ng/mL N=8) renal impairment patients were

105.10% (90%CI: 92.90%, 118.91%) and 111.41% (90%CI: 90.17%, 137.66%), respectively, of those in patients with normal renal function ($C_{trough, ss}$ = 304 ng/mL, N=44). In Study A8081005, the adjusted geometric mean $C_{trough, ss}$ of crizotinib in mild ($C_{trough, ss}$ = 311 ng/mL, N=191) and moderate ($C_{trough, ss}$ = 328 ng/mL, N=65) renal impairment groups were 109.14% (90% CI: 102.08%, 116.68%) and 115.07% (90%CI: 104.08%, 127.23%), respectively, of those in patients with normal renal function ($C_{trough, ss}$ = 285 ng/mL, N=331). The population pharmacokinetic analysis from Studies A8081001, A8081005 and A8081007 indicated that baseline CLcr did not have a clinically relevant effect on crizotinib pharmacokinetics.

An open-label, single dose parallel-group study A8081020 evaluated the effect of severe renal impairment on exposure to crizotinib. Eight subjects with normal renal function (CLcr ≥90 mL/min) were matched 1-to-1 to 8 subjects with severe renal impairment not requiring dialysis (CLcr <30 mL/min) with respect to age (mean 61 vs. 63 years), weight (mean 84 vs. 86 kg) race (6 white and 2 black vs. 5 white and 3 black subjects), and sex (2 males and 6 females in each group). All subjects received a single oral crizotinib dose of 250 mg. The results of Study A8081020 are summarized in Table 7.

Table 7. Statistical Summary of Crizotinib Plasma Exposures by Normal Renal Function and Severe Renal Impairment

Parameter (units)	Adjusted Geometric Means		Ratio (Test/Reference) of Geometric Means[b]	90% CI for Ratio
	Test (Severe Renal Impairment)[a]	Reference (Normal Renal Function)		
AUC_{inf} (ng·hr/mL)	2634	1467	179.48	(126.80, 254.03)
AUC_{last} (ng·hr/mL)	2555	1402	182.18	(128.05, 259.19)
C_{max} (ng/mL)	114.5	85.20	134.34	(99.34, 181.65)

Abbreviation: CI=confidence interval.

a. One subject from severe renal impairment group was excluded in the analysis due to vomit episodes occurring at 1 hour post dose.

b. The ratios (and 90% CIs) are expressed as percentages.

In subjects with severe renal impairment, crizotinib AUC and Cmax increased by 79% and 34%, respectively, compared to those with normal renal function. Based on these results, a starting dose reduction by 50% (250 mg once daily) is recommended when administering crizotinib to patients with severe renal impairment not requiring peritoneal dialysis or hemodialysis (see

WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Special Populations).

No dedicated renal impairment study has been conducted in patients with mild (CLcr 60-89mL/min) or moderate (CLcr 30-59mL/min) renal impairment. Based on the population pharmacokinetic analysis described above, no starting dose adjustment is recommended in patients with mild or moderate renal impairment, although data are limited. Therefore treatment with XALKORI should be used with caution in patients with mild or moderate renal impairment (see WARNINGS AND PRECAUTIONS, and DOSAGE AND ADMINISTRATION). No data are available for patients with end-stage renal disease.

Age: Based on the population pharmacokinetic analysis of pooled PK dataset from Studies A8081001, A8081005 and A8081007 containing 1214 patients with a mean (range) age of 51.8 years (19-83 years), age has no effect on crizotinib pharmacokinetics. Therefore, no starting dose adjustments of crizotinib are recommended based on age.

Ethnicity: After 250 mg twice daily dosing, steady-state crizotinib C_{max} and AUC_{τ} in Asian patients were 1.57- (90% CI: 1.16-2.13) and 1.50- (90% CI: 1.10-2.04) fold those seen in non-Asian patients, respectively. There was a higher incidence of Grade 3 or 4 adverse events in non-Asians (17%) than Asians (10%) (see Clinical Pharmacokinetics section under DETAILED PHARMACOLOGY).

STORAGE AND STABILITY

XALKORI (crizotinib) should be stored at 25°C with excursions to 15-30°C.

SPECIAL HANDLING INSTRUCTIONS

No special requirements.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

XALKORI (crizotinib) 250 mg capsules: Hard gelatin capsule, size 0, pink opaque/pink opaque, with “Pfizer” on the cap and “CRZ 250” on the body.

XALKORI (crizotinib) 200 mg capsules: Hard gelatin capsule, size 1, white opaque/pink opaque, with “Pfizer” on the cap and “CRZ 200” on the body.

Composition

XALKORI capsules are available in two dosage strengths, 250 mg and 200 mg, containing 250 mg and 200 mg of crizotinib, respectively.

Non-Medicinal Ingredients: Colloidal silicon dioxide, microcrystalline cellulose, anhydrous dibasic calcium phosphate, sodium starch glycolate, magnesium stearate, and hard gelatin capsule shells. 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.

Packaging

XALKORI is supplied as bottles of 60 and PVC/aluminum foil blisters containing 60 capsules [6 cards of 10 (5 X 2) capsules].

PART II: SCIENTIFIC INFORMATION

XALKORI (crizotinib), indicated as monotherapy for use in patients with anaplastic lymphoma kinase (ALK)-positive locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC), has been issued marketing authorization with conditions, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the authorization.

PHARMACEUTICAL INFORMATION

Drug Substance

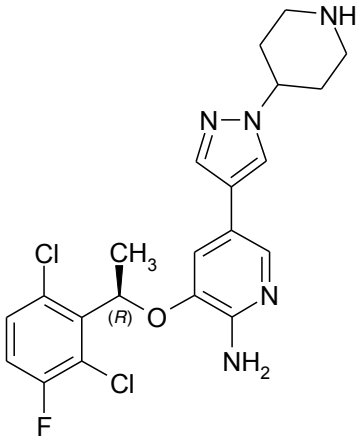
Proper name: Crizotinib

Chemical name: (*R*)-3-[1-(2,6-Dichloro-3-fluorophenyl)ethoxy]-5-[1-(piperidin-4-yl)-1*H*-pyrazol-4-yl]pyridin-2-amine

Code Name: PF-02341066

Molecular formula and molecular mass: $C_{21}H_{22}Cl_2FN_5O$
450.34 Daltons

Structural formula:



Physicochemical properties: 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 is from >10 mg/mL to <0.1 mg/mL. The log of the distribution coefficient (octanol/water) at pH 7.4 is 1.65.

NOC/c CLINICAL TRIALS

ALK-Positive Advanced NSCLC

Randomized Phase 3 Study (Study A8081007)

The use of single-agent XALKORI in the treatment of locally advanced or metastatic ALK-positive NSCLC with or without brain metastases was investigated in a multicenter, multinational, randomized, open-label Phase 3 study (A8081007). The clinical trial was designed as a superiority study that examined XALKORI 250 mg orally twice daily compared to standard-of-care chemotherapy (pemetrexed 500 mg/m^2 or docetaxel 75 mg/m^2) intravenously (IV) every 21 days in patients with ALK-positive advanced NSCLC who had received 1 prior chemotherapy regimen. Patients were required to have ALK-positive NSCLC as identified by FISH prior to randomization. Patients randomized to chemotherapy could cross over to receive XALKORI in Study A8081005 upon RECIST-defined disease progression confirmed by independent radiology review (IRR). The primary efficacy endpoint was Progression-Free Survival (PFS) with disease progression events determined by IRR. Secondary endpoints included Objective Response Rate (ORR) as determined by IRR, Duration of Response (DR), and Overall Survival (OS).

The full analysis population for Study A8081007 included 347 patients with ALK-positive advanced NSCLC. One hundred seventy-three (173) patients were randomized to the XALKORI arm (172 patients received XALKORI) and 174 patients were randomized to the chemotherapy arm (99 [58%] patients received pemetrexed and 72 [42%] patients received docetaxel). Randomization was stratified by ECOG performance status (0-1, 2), brain metastases (present, absent), and prior EGFR tyrosine kinase inhibitor treatment (yes, no). The median duration of study treatment was 31 weeks in the XALKORI arm as compared to 12 weeks in the chemotherapy arm.

Patients could continue treatment as assigned beyond the time of RECIST-defined disease progression, as assessed by IRR, at the discretion of the investigator if the patient was still experiencing clinical benefit.

Key demographic and baseline characteristics for patients in this study were comparable between the XALKORI and chemotherapy arms as shown in Table 8.

Table 8. Demographic and Disease Characteristics in Study A8081007 (Full Analysis Population)

Characteristics	XALKORI N=173	Chemotherapy N=174
Sex, n (%)		
Male	75 (43)	78 (45)
Female	98 (57)	96 (55)
Age (years), n (%)		
Median (range)	51 (22-81)	49 (24-85)
<65 years	146 (84)	151 (87)
>65 years	27 (16)	23 (13)
Race, n (%)		
White	90 (52)	91 (52)
Black	2 (1)	3 (2)
Asian	79 (46)	78 (45)
Other	2 (1)	2 (1)
Smoking status, n (%)		
Never smoked	108 (62)	111 (64)
Ex-smoker	59 (34)	54 (31)
Current smoker	5 (3)	9 (5)
Not reported	1 (<1)	0
Disease Stage		
Locally advanced	7 (4)	16 (9)
Metastatic	165 (95)	158 (91)
Not reported	1 (<1)	0
Histological classification		
Adenocarcinoma	163 (94)	160 (92)
Squamous cell carcinoma	0	3 (2)
Large cell carcinoma	1 (<1)	1 (<1)
Adenosquamous carcinoma	4 (2)	3 (2)
Other	4 (2)	7 (4)
Not reported	1 (<1)	0
Brain Metastases, n (%)		
Present	60 (35)	60 (34)
Absent	113 (65)	114 (66)
Prior EGFR TKI Therapy, n (%)		
Yes	20 (12)	21 (12)
No	153 (88)	153 (88)
ECOG Performance Status, n (%)		
0	72 (42)	65 (37)
1	84 (49)	95 (55)
2	16 (9)	14 (8)
Not reported	1 (<1)	0

XALKORI significantly prolonged PFS compared to chemotherapy as assessed by IRR. The median PFS was 7.7 months for patients randomized to XALKORI and 3.0 months for patients randomized to chemotherapy. The number of PFS events in the XALKORI arm was 100 (58%) of which 84 (84%) were due to objective progression and 16 (16%) were due to death without objective progression and the number of PFS events in the chemotherapy arm was 127 (73%) of which 119 (94%) were due to objective progression and 8 (6%) were due to death without objective progression. The hazard ratio was 0.49 with a p-value of <0.0001 (1-sided log-rank test; HR based on the Cox proportional hazards model stratified by baseline ECOG performance status [0/1 vs 2], presence or absence of brain metastases and presence or absence of prior EGFR TKI treatment). The median PFS for patients treated with XALKORI was 7.7 months and 4.2 months for patients treated with pemetrexed. The hazard ratio was 0.59 with a p-value of 0.0004 (1-sided log-rank test; HR based on the Cox proportional hazards model stratified by baseline ECOG performance status [0/1 vs 2], presence or absence of brain metastases and presence or absence of prior EGFR TKI treatment). The median PFS for patients treated with XALKORI was 7.7 months and 2.6 months for patients treated with docetaxel. The hazard ratio was 0.30 with a p-value of <0.0001 (1-sided log-rank test; HR based on the Cox proportional hazards model stratified by baseline ECOG performance status [0/1 vs 2], presence or absence of brain metastases and presence or absence of prior EGFR TKI treatment).

XALKORI significantly improved IRR-assessed ORR as compared to chemotherapy with a p-value of <0.0001 (2-sided Cochran-Mantel-Haenszel test stratified by baseline ECOG performance status [0/1 vs 2], presence or absence of brain metastases and presence or absence of prior EGFR TKI treatment). The ORR for patients randomized to XALKORI was 65% (95% CI: 58%, 72%) and for patients randomized to chemotherapy was 20% (95% CI: 14%, 26%). The ORR for patients treated with XALKORI was 66% (95% CI: 58%, 73%) and 29% (95% CI: 21%, 39%) for patients treated with pemetrexed, with a p-value of <0.0001 (2-sided Cochran-Mantel-Haenszel test stratified by baseline ECOG performance status [0/1 vs 2], presence or absence of brain metastases and presence or absence of prior EGFR TKI treatment). The ORR for patients treated with XALKORI was 66% (95% CI: 58%, 73%) and 7% (95% CI: 2%, 16%) for patients treated with docetaxel, with a p-value of <0.0001 (2-sided Cochran-Mantel-Haenszel test stratified by baseline ECOG performance status [0/1 vs 2], presence or absence of brain metastases and presence or absence of prior EGFR TKI treatment).

Median DR was 32.1 weeks (95% CI: 26.4 weeks, 42.3 weeks) in the XALKORI arm and 24.4 weeks (95% CI: 15.0 weeks, 36.0 weeks) in the chemotherapy arm.

Overall survival data were not mature at the time of analysis. The median OS was 20.3 months for patients randomized to XALKORI and 22.8 months for patients randomized to chemotherapy. The number of events in the XALKORI arm was 49 (28%) and the number of events in the chemotherapy arm was 47 (27%). The hazard ratio was 1.02 with a p-value of 0.539 (1-sided log-rank test, based on the Cox proportional hazards model stratified by baseline ECOG performance status [0/1 vs 2], presence or absence of brain metastases and presence or absence of prior EGFR TKI treatment).

Efficacy data from Study A8081007 are summarized in Table 9, and the Kaplan-Meier curve for PFS is shown in Figure 1.

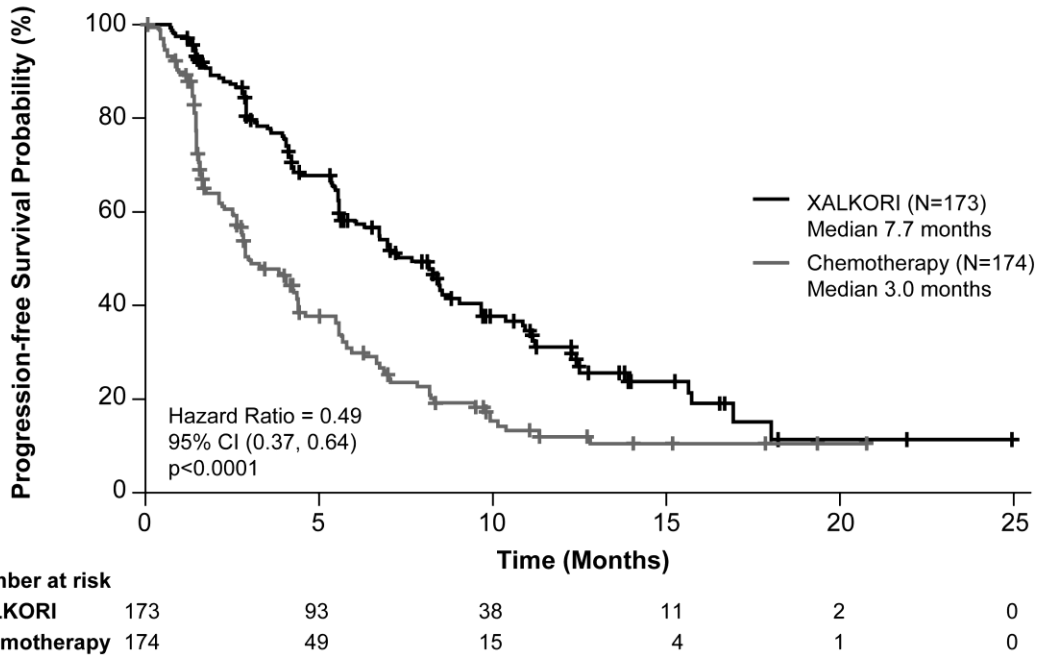
For PFS, the benefit from crizotinib treatment was generally comparable across subgroups of baseline patient characteristics, including ECOG PS, brain metastases, prior EGFR inhibitor treatment group, age, gender, smoking status, histology, duration from primary diagnosis, race group, and extent of disease.

Table 9. ALK-Positive Advanced NSCLC Efficacy Results from Study A8081007 (Full Analysis Population)

Efficacy Parameter	Crizotinib (N=173)	Chemotherapy (N=174)
PFS [median (95% CI)] months	7.7 (6.0, 8.8)	3.0 (2.6, 4.3)
ORR [% (95% CI)]	65 (58, 72)	20 (14, 26)
DR [median (95% CI)] weeks	32.1 (26.4, 42.3)	24.4 (15.0, 36.0)
OS [median (95% CI)] months	20.3 (18.1, NR)	22.8 (18.6, NR)

NR= Not Reached

Figure 1. Kaplan-Meier Curves for Progression-Free Survival by Treatment Arm in Study A8081007 (Full Analysis Population)



Single-Arm Studies in ALK-Positive Advanced NSCLC (Studies A8081001 and A8081005)

The use of single-agent XALKORI (crizotinib) in the treatment of patients with ALK-positive advanced NSCLC with or without brain metastases was investigated in 2 multicenter, multinational, single-arm studies (Study A8081001 and Study A8081005) at a dose of 250 mg BID. Patients enrolled into these studies had received prior systemic therapy, with the exception of 16 patients (13%) in Study A8081001 and 3 patients in Study A8081005 who-had no prior systemic treatment for locally advanced or metastatic disease. Patients received 250 mg of XALKORI orally twice daily.

The primary efficacy endpoint in both studies was ORR according to Response Evaluation Criteria in Solid Tumors (RECIST Version 1.0) as assessed by the investigator.

Secondary endpoints included DR, Time to Tumor Response (TTR), Disease Control Rate (DCR), PFS, and OS. Demographic and disease characteristics for Studies A8081001 and A8081005 are provided in Table 10.

Table 10. Demographic and Disease Characteristics in Single-Arm Studies

Characteristics	Study A8081001 N=119	Study A8081005 N=934
Sex, n (%)		
Male	59 (50)	401 (43)
Female	60 (50)	533 (57)
Age (years), n (%)		
Median (range)	51 (21-79)	52 (19-83)
<65 years	103 (87)	782 (84)
>65 years	16 (13)	152 (16)
Race, n (%)		
White	74 (62)	487 (52)
Black	3 (3)	18 (2)
Asian	34 (29)	409 (44)
Other	8 (7)	20 (2)
Smoking status, n (%)[a]		
Never smoked	86 (72)	618 (66)
Former smoker	32 (27)	279 (30)
Current smoker	1 (<1)	37 (4)
Disease Stage		
Locally advanced	5 (4)	74 (8)
Metastatic	114 (96)	860 (92)
Histological classification		
Adenocarcinoma	116 (98)	880 (94)
Large cell carcinoma	1 (<1)	8 (<1)
Squamous cell carcinoma	1 (<1)	22(2)
Adenosquamous carcinoma	0 (0)	14(1)
Other	1 (<1)	10 (1)
ECOG PS at baseline, n (%)		
0	41 (35)	228 (24)
1	63 (53)	538 (58)
2	14 (12)	133 (14)
3	1 (<1)	35 (4)
Prior Radiation Therapy		
No	51 (43)	413 (44)
Yes	68 (57)	518 (55)
Prior Systemic Therapy for Locally Advanced or Metastatic Disease - Number of Regimens		
0	15 (13)	3 (<1)
1	34 (29)	252 (27)
2	20 (17)	321 (34)
>3	50 (42)	358 (38)

a. Smoking status was determined by the Investigator

ALK-Positive Advanced NSCLC Study A8081001 Results

In Study A8081001, patients with advanced NSCLC were required to have ALK-positive tumors prior to entering the clinical trial. ALK-positive NSCLC was identified using a number of local clinical trial assays. One hundred nineteen (119) patients with ALK-positive advanced NSCLC were enrolled into Study A8081001 at the time of data cutoff. The median duration of treatment was 32 weeks.

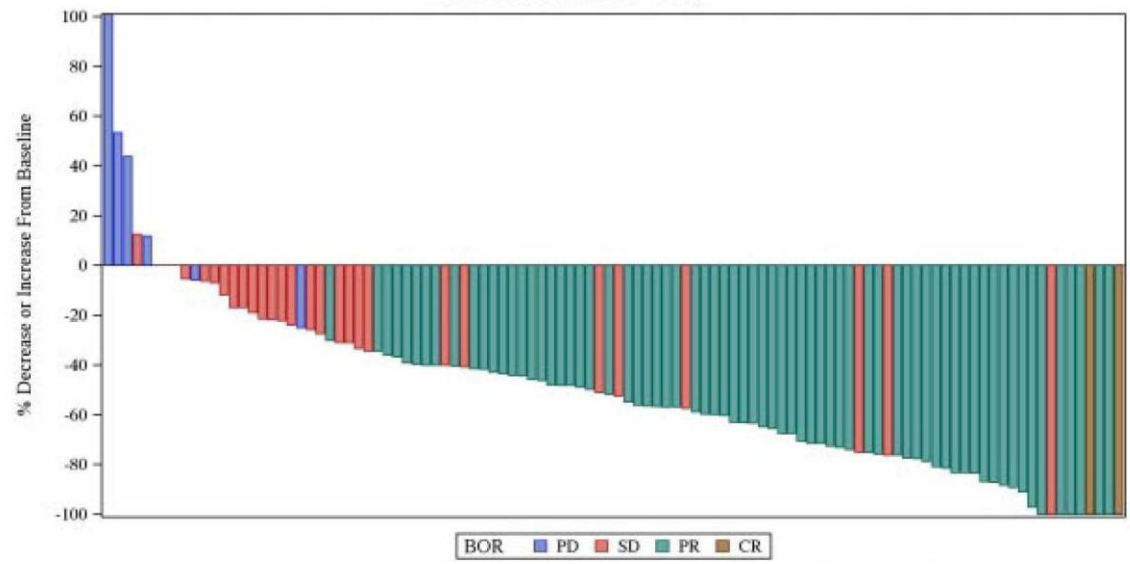
Efficacy data from Study A8081001 are provided in Table 11. There were 2 confirmed complete responses and 69 partial responses for an ORR of 61% (95% CI: 52%, 70%). There were an additional 31 patients who had stable disease for a DCR at 8 weeks of 79%. Fifty-five percent (55%) of objective tumor responses were achieved during the first 8 weeks of treatment. The median DR was 48.1 weeks.

Table 11. ALK-Positive Advanced NSCLC Efficacy Results (Study A8081001)

Efficacy Parameter	**Study A8081001 (N=119)**
ORR[a] [% (95% CI)]	61 (52, 70)
TTR [median (range)] weeks	7.7 (4, 40)
DR [median (range) weeks]	48.1 (4.1+, 76.6+)

[a] Three patients were not evaluable for response
+Censored values

Figure 2. Waterfall Plot of Best Percent Change in Target Lesions from Baseline by Patient Based on Investigator Assessment in Study A8081001 (ALK-Positive NSCLC) (N*=106)



Abbreviations: BOR=best overall response; PD=progressive disease; SD=stable disease; PR=partial response; CR=complete response; N=number of patients; ALK=Anaplastic lymphoma kinase; NSCLC=non-small cell lung cancer; *excludes early death and indeterminate.

Table 12. Study A8081001: ORR by Number of Prior Regimens and ECOG Performance Status (Efficacy Evaluable Population, N=116)

	ORR % (n/N)
No. prior regimens*[#]	
0	80.0 (12/15)
1	57.1 (16/28)
2	61.9 (13/21)
3	59.1 (13/22)
≥4	56.7 (17/30)
ECOG PS	
0	53.8 (21/39)
1	62.9 (39/62)
2	78.6 (11/14)
Race	
Asian	82.4 (28/34)
Non-Asian	52.4 (43/82)

* Prior treatment regimens include any systemic therapy used in the metastatic setting.
[#] Unknown for 1 patient

Note that the benefit of XALKORI in patients with ALK-negative advanced NSCLC has not been established. XALKORI is not recommended for use in patients with ALK-negative NSCLC.

ALK-Positive Advanced NSCLC Study A8081005

In Study A8081005, patients with advanced NSCLC were required to have received at least 1 prior treatment regimen and harbor ALK-positive tumors prior to entering the clinical trial. ALK-positive NSCLC was identified using a Health Canada-approved Vysis ALK break-apart FISH assay.

Nine hundred thirty-four patients with ALK-positive advanced NSCLC were treated with XALKORI in Study A8081005 at the time of data cutoff. The median duration of treatment for these patients was 23 weeks. Patients could continue treatment as assigned beyond the time of RECIST-defined disease progression at the discretion of the investigator if the benefit/risk assessment justified continuation of treatment. Seventy-seven of 106 patients (73%) continued XALKORI treatment for at least 3 weeks after objective disease progression.

Seven hundred sixty-five patients with ALK-positive advanced NSCLC from Study A8081005 were both evaluable for response and identified by the Vysis ALK Break-Apart FISH Probe Kit. Based on investigator assessments, there were 8 complete responses and 357 partial responses for an ORR of 48% (95% CI: 44%, 51%). Eighty-three percent (83%) of objective tumor responses were achieved within the first 12 weeks of treatment. The median DR was 47.3 weeks.

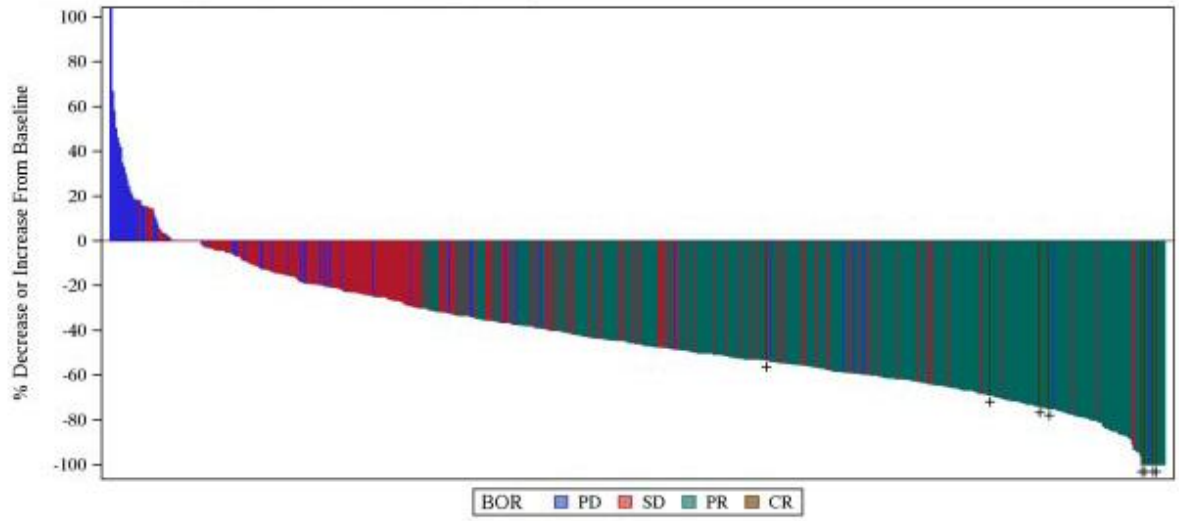
Efficacy data from Study A8081005 are provided in Table 13.

Table 13: ALK-Positive Advanced NSCLC Efficacy Results from Study A8081005

Efficacy Parameter	Study A8081005 (N=765)
ORR[a] [% (95% CI)]	48 (44, 51)
TTR [median (range)] weeks	6.1 (3, 49.1)
DR [median (95% CI) weeks]	47.3 (36, 54)

a. 42 patients were not evaluable for response

Figure 3. Waterfall Plot of Best Percent Change in Target Lesions from Baseline by Patient Based on Investigator Assessment in Study A8081005 Response-Evaluable Population (N* = 660)



N* is based on the RE population(ALK Positive by IUO), excluding patients with Early Death, Indeterminate and those with non-measurable disease only
* Per RECIST 1.1, percent change from baseline for subjects with best overall response of CR can be less than 100% when lymph nodes are included as target lesions.
Patient 10041018 has a percent change from baseline greater than 100%.

DETAILED PHARMACOLOGY

Clinical Pharmacokinetics

Table 14. Descriptive Summary of Plasma Crizotinib Pharmacokinetics Parameters Following 250 mg BID Dosing of Crizotinib in the A8081001 RP2D Cohorts

	Parameter Summary Statistics[a] by Visit			
	Single dose		Multiple dose	
Parameters, Units	**Day -7**	**Cycle 1 Day 1**	**Cycle 1 Day 15**	**Cycle 2 Day 1**
N	46	98	24	18
T_{max}, hr	4.00 (2.00-9.33)	4.05 (1.00-9.08)	4.00 (0.00-9.03)	4.00 (0.00-9.02)
C_{max}, ng/mL	108 (38)	98.9 (45)	411 (44)	478 (38)
C_{trough}, ng/mL	0.00 (0.00-32.6)[b]	0.00 (0.00-517)[c]	319 (1.57-1030)[d]	301 (3.17-849)[e]
AUC_{τ}, ng*hr/mL	742 (40)	663 (45)[f]	3880 (36)[g]	4164 (38)[h]
AUC_{inf}, ng*hr/mL	2489 (51)[i]	NA	NA	NA
CL/F, L/hr	100 (50)[i]	NA	64.5 (56)[g]	60.1 (44)[h]

Abbreviations: N=number of patients; NA=not applicable; AUCτ =area under the plasma concentration-time profile from zero time to time τ; CV=coefficient of variation; T_{max}=time of maximum observed concentration; C_{trough}=trough (predose) concentration; AUC_{inf}=area under the plasma concentration-time profile from zero time to infinity; BID=twice daily; RP2D=recommended Phase 2 dose

a. Geometric mean (%CV) for all except: median (range) for T_{max} and C_{trough}

b. n=43; [c] n=160; [d] n=109; [e] n=91; [f] n=88; [g] n=19; [h] n=16; [i] n=29

Drug Interactions

Potential to Inhibit CYP Enzymes CYP1A2, CYP2C8, CYP2C9, CYP2C19 and CYP2D6

In vitro studies with pooled human liver microsomes and specific CYP probe substrates indicated that the IC_{50} for CYP2C9 was 23 μM (10,400 ng/mL) and >30 μM (13,500 ng/mL) for CYP1A2, CYP2C8, CYP2C19 and CYP2D6. Clinical interactions with substrates of CYP1A2, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 are unlikely to occur considering the potency of crizotinib to inhibit these enzymes and the mean total crizotinib plasma concentration at C_{max} (411 ng/mL, 0.91 μM) following therapeutic doses of 250 mg BID in patients with cancer, as C_{max}/IC_{50} values were <0.1 for these 5 CYP enzymes.

Potential to Induce CYP Enzymes

The potential for crizotinib to induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4 enzymes was evaluated in a series of in vitro studies using human cryopreserved hepatocytes (3 lots) incubated with crizotinib at concentrations up to 7 μM (3150 ng/mL). Crizotinib caused marked induction of CYP3A4 based on mRNA levels; however, a corresponding induction of CYP3A4 enzyme activity was not observed. This finding is likely due to the crizotinib-mediated time-dependent inhibition of CYP3A4. Crizotinib did not induce CYP1A2 enzyme activity. Crizotinib did not cause induction of CYP2B6 enzyme activity or mRNA expression. A trend toward decreased CYP2B6 activity in hepatocytes treated with

increasing concentrations of crizotinib was observed, which is consistent with crizotinib-mediated time-dependent inhibition of CYP2B6. Moreover, crizotinib did not cause induction of CYP2C8, CYP2C9 or CYP2C19 enzyme activity or of CYP2C9 mRNA expression. Crizotinib-mediated induction of CYP2C8 mRNA expression was observed in 1 of 3 lots evaluated without a corresponding induction of enzyme activity. Due to the lack of induction of CYP2C19 mRNA with the positive control inducer rifampin, mRNA expression was not deemed to be a reliable endpoint for assessment of CYP2C19 induction. Based on the collective results of these in vitro studies, crizotinib is not expected to reduce plasma concentrations of co-administered drugs that are substrates of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A.

Potential to Inhibit UGT Enzymes

In an in vitro study with pooled human liver microsomes and specific UGT probe substrates, the IC_{50} values for crizotinib-mediated inhibition of UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7 were 11, 20, 41, 47, and 21 μM, respectively, in the absence of bovine serum albumin (BSA) and 33, >60, >60, >60, and 43 μM, respectively, in the presence of BSA. The highest potency for crizotinib-mediated UGT inhibition was for UGT1A1 and UGT2B7, in the presence of BSA, with free IC_{50} values of 5.3 μM and 6.9 μM, respectively (unbound fraction in BSA of 0.16). Based on the basic DDI models outlined in the draft FDA guidance (2012) and EMA guideline (2012), clinical metabolic DDIs resulting from crizotinib-mediated inhibition of the metabolic clearance of concomitant drugs that are substrates for UGT1A1 and UGT2B7 cannot be excluded.

Potential to Inhibit Hepatic Uptake Transporter OCT1 and Renal Uptake Transporter OCT2

Crizotinib was evaluated for its potential to inhibit human organic cation transporter 1 (OCT1) and 2 (OCT2) when expressed in human embryonic kidney (HEK) 293 cells. Crizotinib demonstrated concentration-dependent inhibition of OCT1 and OCT2, with calculated IC_{50} values of 2.4 μM and 0.22 μM, respectively. Based on the DDI criteria outlined in the draft FDA guidance (2012) for OCT2 and EMA guideline (2012) for OCT1 and OCT2, crizotinib has the potential to inhibit OCT1 and OCT2 at clinically relevant drug concentrations, and thus, there is the potential for DDIs with concomitant drugs that are substrates for these transporters.

Potential to Inhibit Hepatic Uptake Transporters OATP1B1 and OATP1B3

Crizotinib-mediated inhibition of hepatic transporters OATP1B1 and OATP1B3 was evaluated in vitro in studies using cell lines expressing these human transporters and specific OATP probe substrates. Crizotinib demonstrated a weak, concentration-dependent inhibitory effect on pravastatin (OATP1B1 substrate) and rosuvastatin (OATP1B3 substrate) uptake, with IC_{50} values of 48 and 44 μM, respectively. Clinical interactions with substrates of OATP1B1 and OATP1B3 are unlikely to occur as the concentration of crizotinib that inhibits 50% of OATP-mediated transport greatly exceeds the mean unbound crizotinib plasma concentration at C_{max} (38 ng/mL, 0.085 μM) and estimated maximum crizotinib concentration in liver following therapeutic doses of 250 mg BID in patients with cancer.

Potential to Inhibit Renal Uptake Transporters OAT1 and OAT3

Crizotinib was evaluated for its potential to inhibit the human renal organic anion transporters 1 and 3 (OAT1, OAT3) when expressed in Chinese Hamster Ovary (CHO) cells. Crizotinib did not inhibit either OAT1- or OAT3-mediated transport of probe substrates at any concentration evaluated (up to 32 μM). Therefore, clinical drug-drug interactions are unlikely to occur as a result of crizotinib-mediated inhibition of the renal uptake of drugs that are substrates for these transporters.

Non-Clinical Pharmacokinetics

Tissue distribution of total [^{14}C]crizotinib-derived radioactivity was evaluated in Long-Evans (pigmented) male rats after a single oral dose (10 mg/kg) of [^{14}C]crizotinib. Crizotinib-derived radioactivity exhibited a prominent affinity for pigmented tissues (e.g., ocular tissues, excluding the lens of the eye; pigmented skin). Crizotinib radioequivalents declined slowly from the eye with an estimated elimination $t_{1/2}$ of 24 days (576 hours), indicating that the association appeared to be reversible. Likewise, pigmented skin concentrations of radioactivity declined more slowly relative to non-pigmented skin. Affinity to pigmented tissues is commonly observed for lipophilic basic compounds, like crizotinib, and is due to reversible binding to melanin. Melanin binding is not directly predictive of ocular toxicity.

Non-Clinical Pharmacology

The non-clinical pharmacology program of crizotinib evaluated safety, pharmacokinetics, toxicology and the ability of crizotinib to inhibit the activity and function of its receptor tyrosine kinase (RTK) targets *in vitro* and *in vivo* as well as its ability to inhibit tumor progression in rodent models of experimental cancer.

Primary Pharmacodynamics

In Vitro

Crizotinib demonstrated concentration-dependent inhibition of the kinase activity of ALK and c-Met in biochemical assays and inhibited phosphorylation and kinase dependent phenotypes in cell-based assays. Crizotinib demonstrated potent and selective growth inhibitory activity and induced apoptosis in tumor cell lines exhibiting ALK fusion events (EML4-ALK or NPM-ALK) or exhibiting amplification of the *ALK* or *MET* gene locus. Crizotinib metabolites formed via major human biotransformation pathways have also been identified and crizotinib lactam metabolites exhibit potentially pharmacologically relevant inhibitory activity and potentially contribute to ALK and c-Met if present at adequate levels in humans. Crizotinib potently inhibited the catalytic activity of ROS1 kinase with a mean K_i of 0.48 nM. Crizotinib inhibited the autophosphorylation of CD74-ROS1 (s), SLC34A2-ROS1 (s/L), Fig-ROS1, and Fig-ROS1 (s/L) in the human NSCLC, glioblastoma and the NIH3T3 cell lines engineered to express selected variants of human oncogenic ROS1 fusion proteins with EC_{50} values ranging from 11 nM to 104 nM. Crizotinib also inhibited cell proliferation (EC_{50} = 46 nM) and induced cell apoptosis in the SLC34A2-ROS1 fusion positive HCC78 NSCLC cells. These effects of

crizotinib on cancer cell phenotypes were strongly correlated with the inhibition of ROS1 kinase activity and ROS1 mediated signal transduction in these cells.

In Vivo

Crizotinib demonstrated antitumor efficacy, including marked cytoreductive antitumor activity, in mice bearing tumor xenografts that expressed ALK fusion proteins. The antitumor efficacy of crizotinib was dose-dependent and correlated to pharmacodynamic inhibition of phosphorylation of ALK fusion proteins (EML4-ALK or NPM-ALK) in tumors *in vivo*. Crizotinib demonstrated marked antitumor activity (tumor growth inhibition [TGI] and tumor growth regression) in a panel of engineered NIH-3T3-ROS1 xenograft models at well-tolerated dose levels. The antitumor efficacy of crizotinib was dose-dependent and demonstrated a correlation to inhibition of ROS1 phosphorylation *in vivo*. PKPD modeling was conducted to understand the relationships between crizotinib plasma concentration to antitumor activity in the NIH-3T3-CD74-ROS1 (s) and the NIH-3T3-SLC34A2-ROS1 (L) xenograft studies. The modeling results suggest that achieving a free plasma concentration of 84 nM to 99 nM was required to achieve 100% TGI in these 2 ROS1 fusion driven xenograft models. Collectively, the combination of studies in the NIH-3T3-CD74-ROS1 (s) and the NIH-3T3-SLC34A2-ROS1 (L) xenograft models indicated that the extent of the inhibition in ROS1 activity was directly linked to the level of antitumor activity, and that significant inhibition of ROS1 kinase activity during the entire dosing period was necessary to achieve robust antitumor activity (i.e., complete TGI). PK/PD modeling was performed to calculate unbound plasma concentrations required for inhibition of ALK and c-Met phosphorylation and antitumor efficacy *in vivo* and data are summarized in Table 15 below.

Table 15. Summary of Selected Key Crizotinib Pharmacological Properties

Assay	Crizotinib Concentration	
	nM	ng/mL
Biochemical Activity *In Vitro*		
ALK enzyme (mean Ki, nM)	0.5	0.2
c-Met/HGFR enzyme (mean Ki, nM)	0.6	0.3
ROS1 enzyme (mean Ki, nM)	0.48	0.2
Cellular Activity *In Vitro*		
EML4-ALK V1 phosphorylation in NCI-H3122 human lung adenocarcinoma cells (mean EC_{50})	63	28
EML4-ALK V3 phosphorylation in NCI-H2228 human lung adenocarcinoma cells (mean EC_{50})	74	33
c-Met/HGFR phosphorylation in human tumor cell lines (mean EC_{50})	11	5
ALK phosphorylation in NCI-H3122 tumors		
PK/PD model (Link model) of PO administration (unbound plasma EC_{50})	19	8.4
Tumor growth inhibition of NCI-H3122 tumors		
PK/PD models (indirect response model) (mean unbound plasma EC_{50})	23	10
c-Met/HGFR phosphorylation in GTL-16 tumors		
PK/PD models (Shiner model) of PO administration (mean unbound plasma EC_{50})	1.0	0.4
Subcutaneous infusion (unbound plasma EC_{50})	2.8	1.2
PK/PD models (Shiner model) of PO administration (mean unbound plasma EC_{90})	12.8	5.8
Subcutaneous infusion (EC_{90})	8.1	3.7
Tumor growth inhibition in ROS1 driven models		
NIH-3T3-CD74-ROS1 (s) (PO; mean unbound plasma; 100% TGI)	99	45
NIH-3T3-SLC34A2-ROS1 (L) (PO; mean unbound plasma; 100% TGI)	84	38

Secondary Pharmacodynamics

Crizotinib displayed functional antagonism of the 5-HT_{4e} (K_b 140 nM; 63 ng/mL), 5-HT_7 (K_b 2.2 μM; 991 ng/mL) and α_{1a} adrenergic (K_b 40.7 nM; 18.3 ng/mL) receptors. Crizotinib was also identified as an inhibitor of dopamine and 5-HT uptake (IC_{50} of 630 and 830 nM [284 and 374 ng/mL], respectively).

Safety Pharmacology

Crizotinib is a mixed ion channel inhibitor. Crizotinib inhibited currents (IC_{20} of 300 nM; 135 ng/mL) in HEK293 cells stably expressing human ether-à-go-go-related gene (hERG) potassium channels. Crizotinib inhibited cardiac L-type calcium channel currents ($I_{Ca,L}$) in isolated guinea pig ventricular myocytes (IC_{50} of 14.6 μM; 6575 ng/mL) and relaxed rat isolated aortic rings pre-contracted with 45 mM KCl (IC_{50} of 0.83 μM; 374 ng/mL), indicating that crizotinib is a calcium channel antagonist. These values are ≥4-fold above crizotinib concentrations (free drug) after 250 mg BID repeated dosing in patients.

Crizotinib is also an inhibitor of the Nav1.1 sodium channel stably expressed in HEK293 (IC_{50} of 850 or 870 nM [383 or 392 ng/mL] for the closed or inactivated state, respectively), and Nav1.5 sodium channel stably expressed in Chinese Hamster Ovary cells (IC_{10} of 250 nM; 113 ng/mL).

Inhibitory concentration estimates for hERG, Nav 1.1 and 1.5 sodium channels, and L-type calcium channels are based on nominal concentrations.

Cardiovascular effects (decreased blood pressure, heart rate, and myocardial contractility) were observed in an anesthetized cardiovascular dog study at unbound plasma concentrations ≥84 ng/mL following repeat-dose administration (approximately 2 times the human clinical exposure based on C_{max}). Increases in left ventricular end diastolic pressure (LVEDP), and QT, QRS, and PR interval durations were also observed at ≥84 ng/mL. QT interval changes were considered secondary to the effect of crizotinib on heart rate.

In safety pharmacology studies, there were no crizotinib-related neurofunctional or respiratory effects in rats following the administration of single oral doses of up to 500 mg/kg in rats.

TOXICOLOGY

Animal Toxicology

The non-clinical toxicologic profile of crizotinib has been extensively investigated in the rat and dog. The primary target organ findings observed following repeat-dose administration were in the gastrointestinal, hematopoietic, hematological, liver (elevated liver transaminases), and reproductive organs. Gastrointestinal effects were observed clinically as emesis and abnormal feces (soft, mucoid, or watery/diarrhea) in the dog at doses of 5 up to 25 mg/kg/day without a histological correlate in studies up to 3 months in duration (sub-therapeutic to 2 times the human clinical exposure based on AUC). Bone marrow hypocellularity (myeloid and erythroid) or cellular debris evident of toxicity was noted following ≥1 month of dosing in the rat at doses ≥30 mg/kg/day (approximately equivalent to human clinical exposure based on AUC). Elevations of liver transaminases (alanine aminotransferase, aspartate aminotransferase, and/or gamma glutamyltransaminase) occurred without evidence of a histological correlate in studies of up to 3 months duration at doses of 10 to 250 mg/kg/day in the rat and 5 to 25 mg/kg/day in the dog (sub-therapeutic to 3 times the human clinical exposure based on AUC). Effects on male and female reproductive organs included testicular pachytene spermatocyte degeneration at ≥50 mg/kg/day (approximately equivalent to human clinical exposure based on AUC) and single cell necrosis of ovarian follicles of a single rat given 500 mg/kg/day for 3 days (exposure not evaluable). The gastrointestinal, hematopoietic, liver, and reproductive effects observed following 3 months of dosing were shown to be reversible.

Dose-limiting toxicity resulting in mortality occurred in rats (250 mg/kg/day in a 90-day study, 500 mg/kg/day in a 7-day study and 2000 mg/kg/day in a 2-day study and dogs (up to 40 mg/kg/day in a 7-day dose escalation study).

Other crizotinib-related findings observed in the rat included decreased body weight and food consumption, an effect on retinal function, salivary glands, and actively growing long bones, and of unclear clinical relevance was phospholipidosis in multiple organs and the observation of significantly higher exposures (1.6-2.9-fold) in male rats (1-month and 3-month repeat-dose

studies) with a similar trend observed in a 7-day dog study. A reduced rate of dark adaptation was identified in rats from electroretinography measurements following 2 and 4 weeks of dosing at 100 mg/kg/day (approximately 3 times human clinical exposure based on AUC). Swelling of salivary gland mucous cells at 100 mg/kg/day following 3 months of dosing in the rat (approximately 3 times human clinical exposure based on AUC) was found to be partially reversible after a 2-month recovery period. Decreased bone formation in growing long bones was observed in immature rats at 150 mg/kg/day following 28 days of dosing (approximately 3 times human clinical exposure based on AUC). Phospholipidosis of multiple organs (kidneys, bile duct, intestine, pituitary gland, prostate, lung, and/or mesenteric lymph node) was identified in the rat following 1 or 3 months of dosing at 30 to 250 mg/kg/day (approximately equivalent to 3 times human clinical exposure based on AUC). After a 2-month recovery period, full reversibility of phospholipidosis was observed in all tissues except the prostate and mesenteric lymph node (kidney not evaluated), where foamy macrophages were noted with decreased incidence, severity and/or distribution.

Carcinogenesis, Mutagenesis, Phototoxicity, Reproductive and Developmental Toxicity

Carcinogenicity studies with crizotinib have not been performed.

Crizotinib demonstrated genotoxicity in a human lymphocyte chromosome aberration assay (*in vitro*) and rat bone marrow micronucleus assay (*in vivo*). A positive kinetochore assay suggests an aneugenic mechanism. A no effect level for aneugenicity was identified at 100 mg/kg/day (approximately 2 times the human clinical exposure based on AUC). Crizotinib is not considered a mutagen based on negative results in bacterial reverse mutation assays.

Crizotinib may have phototoxic potential based on a photo-irritation factor (PIF) of 3.4 in an in vitro 3T3 fibroblast Neutral Red Uptake assay. Therefore, it is recommended that patients minimize their exposure to sunlight and other UV emitting sources.

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 $\geq$50 mg/kg/day for 28 days (approximately equivalent to human clinical exposure 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 for 3 days.

Crizotinib was not shown to be teratogenic in pregnant rats or rabbits. Reduced fetal body weights were considered adverse effects in the rat and rabbit at 200 and 60 mg/kg/day, respectively (approximately equivalent to human clinical exposure based on AUC).

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PART III: CONSUMER INFORMATION

XALKORI, for use in patients with lung cancer having specific change in a gene called ALK, has been approved with conditions, pending the results of studies to verify its clinical benefit. For more information, patients are advised to contact their health care provider.

What is a Notice of Compliance with Conditions (NOC/c)?
An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products approved under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

PrXALKORI™
Crizotinib Capsules

This leaflet is part III of a three-part "Product Monograph" published when XALKORI was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about XALKORI. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
XALKORI (crizotinib) is used to treat patients with anaplastic lymphoma kinase (ALK)-positive locally advanced (a cancer that cannot be surgically removed for cure) or metastatic (a cancer that has spread to other parts of the body) non-small cell lung cancer (NSCLC) that is a type of lung cancer with a defective gene.

Patients should have their cancer tested and confirmed for ALK-positive NSCLC before receiving treatment with XALKORI.

What it does:
XALKORI may slow or stop the growth of lung cancer. It may help shrink tumors.

When it should not be used:
Do not take XALKORI:

- If you have congenital long QT syndrome – a heart disorder that exists before or at birth.
- If you are allergic (hypersensitive) to crizotinib or any of the other ingredients of XALKORI, listed under "**What the nonmedicinal ingredients are:**"

What the medicinal ingredient is:
Crizotinib.

What the nonmedicinal ingredients are:
Silicon dioxide, microcrystalline cellulose, calcium phosphate dibasic anhydrous, sodium starch glycolate, magnesium stearate. **Pink opaque hard gelatin capsule shell:** gelatin, titanium dioxide, red iron oxide. **White opaque hard capsule shell:** gelatin, titanium dioxide. **Printing ink:** shellac, propylene glycol, strong ammonia solution, potassium hydroxide and black iron oxide.

What dosage forms it comes in:
XALKORI is available as 250 mg and 200 mg capsules. The 250 mg capsule is a pink opaque/pink opaque hard gelatin capsule with "Pfizer" on the cap and "CRZ 250" on the body. The 200 mg is a white opaque/pink opaque hard gelatin capsule with "Pfizer" on the cap and "CRZ 200" on the body.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

XALKORI should be prescribed and used under the supervision of a doctor experienced with drugs used to treat cancer.

Serious side effects with XALKORI include:

- QT interval prolongation, and very slow heart rate (bradycardia)
- Serious lung diseases such as interstitial lung disease (that can cause trouble breathing or shortness of breath, cough or fever) or pneumonitis that may result in death
- Liver toxicity that may result in death

XALKORI has not been studied in patients with liver impairment or severe kidney impairment needing hemodialysis.

XALKORI decreases heart rate and has an effect on the electrical activity of the heart known as QT interval prolongation. These effects can be measured as changes in the electrocardiogram (ECG). Drugs with these effects on the ECG can lead to disturbances in heart rhythm (arrhythmias/dysrhythmias) that could result in dizziness, palpitations (sensation of rapid, pounding, or irregular heartbeat), fainting, or death. These heart rhythm disturbances are more likely in patients with risk factors, such as heart disease, or in the presence of certain interacting drugs. It is important to follow the instructions of your doctor with regard to dosing or any special tests. You may need to have electrocardiograms (ECGs) and blood tests to measure your levels of potassium, calcium, and magnesium at regular intervals during treatment with XALKORI. If you experience any symptoms of a possible heart rhythm disturbance, such as dizziness, palpitations (sensation of rapid, pounding, or irregular heartbeat), fainting, or seizures, you should seek immediate medical attention.

XALKORI may cause inflammation of the lungs during

treatment. This condition may be similar to lung cancer. Tell your doctor or nurse right away if you have any new or worsening symptoms, including difficulty breathing, cough, or fever.

BEFORE you use XALKORI talk to your doctor or pharmacist if:

- You have any heart disorder, including an irregular heartbeat, an abnormal electrical signal called "prolongation of the QT interval" or a family history of QT interval prolongation or sudden cardiac death at <50 years of age;
    - You have a personal history of fainting spells;
    - You have electrolyte disturbances (e.g., low blood calcium, potassium, or magnesium levels) or conditions that could lead to electrolyte disturbances (e.g., vomiting, diarrhea, dehydration);
    - You have an eating disorder or are following a strict diet;
    - You have diabetes, especially with associated nerve disorders
- You have liver or kidney problems
- You have symptoms of nerve damage (peripheral neuropathy) such as pain, burning, or numbness
- You have eye problems
- You are pregnant, or planning to become pregnant
- Do not breastfeed while using XALKORI, it is not known if the drug can get into the breast milk, and therefore, into the baby.

XALKORI may cause harm to your unborn baby. Both male and female patients must use an effective birth control method while taking XALKORI and for at least 90 days after the last dose. If you or your partner become pregnant, tell your doctor right away.

Male and female fertility may be affected by treatment with XALKORI.

The use of XALKORI in people younger than 18 years old has not been established.

Do not drive or operate machinery if you feel tired or dizzy, or experience any change in vision while taking XALKORI.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist about all the medicines you take including prescription medicines, over-the-counter drugs, vitamins, and herbal products. Some medicines can react with XALKORI and may cause serious side effects or may change the amount of XALKORI in your body. You are still able to receive immunizations while taking crizotinib.

Especially tell your doctor if you take:

- Medicines that may affect your heartbeat such as :
    - medicines for heart rhythm problems (anti-arrhythmics) such as quinidine, amiodarone
    - medicines for depression such as amitryptyline and imipramine
    - medicines for psychoses such as pimozide, ziprasidone, and haloperidol
    - medicines for infections (antibiotic) such as azithromycin, clarithromycin, moxifloxacin, and ciprofloxacin
    - medicines for fungal infection such as ketoconazole and itraconazole
    - medicines to treat malaria such as quinine and chloroquine
    - medicines for nausea and vomiting such as ondansetron, domperidone, and dolasetron
    - methadone
    - pentamidine
    - other cancer medicines such as sunitinib, nilotinib, lapatinib, and vandetanib
    - asthma drugs such as formoterol and salmeterol
    - medicines that decrease electrolyte levels (water pills, laxatives)
    - some medicines for high blood pressure, which may also decrease the heart rate-such as verapamil, diltiazem, and atenolol
- HIV medicines such as atazanavir, saquinavir, ritonavir and indinavir
- Other antibiotics such as rifampin and rifabutin
- St. John's wort

Keep a list of your medicines. Show it to your doctor or pharmacist. Talk with your doctor before starting any new medicines.

PROPER USE OF THIS MEDICATION

Usual Dose:

- 250 mg taken by mouth twice daily, unless instructed otherwise by your doctor. Do not crush, dissolve or open the capsules. The capsules can be taken with or without food.
- Do not drink grapefruit juice or eat grapefruit, or products containing grapefruit extracts, star fruit, pomegranate, Seville oranges or other similar fruits. They may change the amount of XALKORI in your body.

Overdose:

If you take more XALKORI than you should, or in case of drug overdose, contact a health care practitioner, or hospital emergency department, or a Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose, take it as soon as you remember. Do not take it if it is less than 6 hours until the next dose. Just take the next dose at your regular time. Do not take more than 1 dose of XALKORI at a time. Tell your doctor or nurse about the missed dose at your next visit.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Possible serious side effects include:

- **Heart tracing abnormality that could lead to heart rhythm disturbance – Tell your doctor or nurse right away if you experience dizziness, fainting, palpitations (irregular heartbeat), seizures, or chest discomfort.**
- **Liver problems – Tell your doctor or nurse right away if you are feeling more tired than usual, your skin and whites of your eyes turn yellow, if you experience stomach pain, your urine turns dark or brown (tea color), you have nausea or vomiting, you have decreased appetite, you bleed or bruise more easily than normal, or if you have itching.**
- **Lung inflammation – Tell your doctor or nurse right away if you have any new or worsening symptoms including difficulty breathing, cough or fever.**

Very common side effects (these are likely to affect more than 10 in every 100 people):

- Nausea, diarrhea, vomiting, constipation, swelling of the hands and feet, tiredness, dizziness, neuropathy (symptoms include numbness, prickling or tingling, burning, freezing, throbbing and/or shooting pain), change of taste, decreased appetite, abnormal liver enzymes, cough, shortness of breath, respiratory infections (such as tonsillitis, pharyngitis, laryngitis, and sinusitis), chest pain, abdominal pain, low red and white blood cell count, headache, fever, mouth ulcers, back pain, and rash.
- Visual changes such as perceived flashes of light, blurry vision, and double vision. They most commonly began soon after starting treatment with XALKORI.

Common side effects (these are likely to affect between 1 and 10 in every 100 people):

- Low heart rate, upset stomach, and low blood pressure. Talk with your doctor about ways to handle these problems.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / Effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common (≥1% to <10%)	**Lung inflammation: difficulty breathing, cough or fever**		✓	
	Infection of the lung (pneumonia)		✓	
	Vomiting	✓		
Uncommon (≥0.1% to <1%)	**Heart tracing abnormality that could lead to heart rhythm disturbance: dizziness, fainting, or chest discomfort**		✓	
	Liver problems: feeling more tired than usual, skin and whites of eyes turn yellow, stomach pain, urine turns dark or brown (tea color), nausea or vomiting, decreased appetite, bleed or bruise more easily than normal, or itching		✓	
	Fever associated with a marked decrease in the number of neutrophils (a type of white blood cells)		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / Effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / Effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
	Closed pouches of fluid within the kidneys (complex kidney cysts): includes symptoms such as pain in the back or side and blood in urine		✓	

This is not a complete list of side effects. For any unexpected effects while taking XALKORI, contact your doctor or pharmacist.

HOW TO STORE IT

- Keep XALKORI and all medicines out of the reach of children.
- Store XALKORI at room temperature at 25°C (with excursions between 15°C to 30°C). Do not touch or handle crushed or broken XALKORI capsules. XALKORI is formulated with a capsule to prevent contact with the active ingredient.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals can be found at:
http://www.pfizer.ca
or by contacting the sponsor, Pfizer Canada Inc., at:
1-800-463-6001.

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