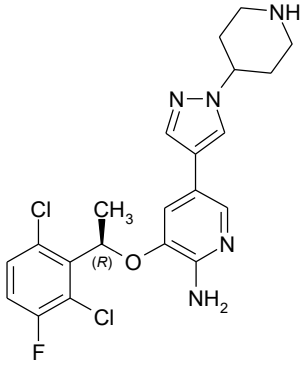
PT. PFIZER INDONESIA
Local Product Document

Generic Name: Crizotinib
Trade Name: XALKORI®
CDS Effective Date: June 02, 2022
Supersedes: July 03, 2019

NAME OF THE MEDICINAL PRODUCT
XALKORI 200 mg; XALKORI 250 mg

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains either 200 mg or 250 mg of crizotinib.

Excipients: see Section **List of Excipients** for a full list of excipients.



Crizotinib is a white to pale yellow powder with a pKa of 9.4 (piperidinium cation) and 5.6 (pyridinium cation).

PHARMACEUTICAL FORM
Hard gelatin capsules

CLINICAL PARTICULARS
Therapeutic Indications
Crizotinib is indicated for the treatment of adults with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).

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

Crizotinib is indicated for the treatment of ROS1-positive advanced NSCLC.

Crizotinib should be prescribed by a qualified healthcare professional who is experienced in the use of anti-neoplastic therapy.

Posology and Method of Administration

ALK and ROS1 testing

Detection of either ALK-positive or ROS1 positive NSCLC is necessary for selection of patients for treatment with crizotinib because these are the only patients for whom benefit has been shown.

Assessment for either ALK-positive or ROS1 positive NSCLC should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. Improper assay performance can lead to unreliable test results.

Recommended dosing

The recommended dose schedule of crizotinib is 250 mg taken orally twice daily. Continue treatment as long as the patient is deriving clinical benefit from therapy. Crizotinib may be taken with or without food (see Section **Pharmacokinetic Properties**). The capsules should be swallowed whole preferably with water, and should not be crushed, dissolved, or opened. They may be taken with or without food. Grapefruit or grapefruit juice should be avoided since it may increase crizotinib plasma concentration; St. John's wort should be avoided since it may decrease crizotinib plasma concentration. If a dose of crizotinib is missed, then it should be taken as soon as the patient remembers unless it is less than 6 hours until the next dose, in which case the patient should not take the missed dose. Patients should not take 2 doses at the same time to make up for a missed dose.

Dose modification

Dosing interruption and/or dose reduction may be required based on individual safety and tolerability. If dose reduction is necessary for patients treated with crizotinib 250 mg orally twice daily, then the dose of crizotinib should be reduced as below.

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

Dose reduction guidelines for hematologic and non-hematologic toxicities are provided in Table 1 and Table 2. For patients treated with a lower dose of crizotinib than 250 mg twice daily, then use the recommendations in Table 1 and Table 2 accordingly.

Table 1. Crizotinib Dose Modification – Hematologic Toxicities[a]

CTCAE[b] Grade	Crizotinib 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 the next lower dose[c,d]

[a] Except lymphopenia (unless associated with clinical events, e.g. opportunistic infections).
[b] National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events.
[c] In case of recurrence, withhold until recovery to Grade ≤2, then resume at 250 mg, once daily. Permanently discontinue in case of further Grade 4 recurrence.
[d] For patients treated with 250 mg once daily or whose dose was reduced to 250 mg once daily, discontinue during evaluation.

Table 2. Crizotinib Dose Modification – Non-hematologic Toxicities

CTCAE[a] Grade	Crizotinib Dosing
Grade 3 or 4 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation with Grade ≤1 total bilirubin	Withhold until recovery to Grade ≤1 or baseline, then resume at the next lower dose.[b,c]
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[d]	Permanently discontinue
Grade 3 QTc prolongation	Withhold until recovery to Grade ≤1, then resume at the next lower dose.[b,c]
Grade 4 QTc prolongation	Permanently discontinue.
Grade 2, 3 bradycardia[e] (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 antihypertensive 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[e] upon recovery to Grade ≤1 or to heart rate of 60 bpm or above.

Grade 4 bradycardia[e,f] (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[c] 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, then resume at 250 mg, once daily. Permanently discontinue in case of further Grade 3 or 4 recurrence.
[c] For patients treated with 250 mg once daily or whose dose was reduced to 250 mg once daily, discontinue during evaluation.
[d.] Not attributable to NSCLC progression, other pulmonary disease, infection, or radiation effect.
[e.] Heart rate less than 60 beats per minute (bpm).
[f.] Permanently discontinue for recurrence.

Hepatic impairment:
Crizotinib is extensively metabolized in the liver. Treatment with crizotinib should be used with caution in patients with hepatic impairment (see Table 2 and Sections **Special Warnings and Precautions for Use** and **Pharmacokinetic Properties**).

A clinical study was conducted in patients with advanced cancer and varying degrees of hepatic impairment, based on National Cancer Institute (NCI) classification, who received multiple doses of crizotinib to evaluate the effect of hepatic impairment on the pharmacokinetics and safety of crizotinib.

No starting dose adjustment of crizotinib is recommended for patients with mild hepatic impairment (either AST > Upper Limit of Normal (ULN) and total bilirubin ≤ULN or any AST and total bilirubin >ULN but ≤1.5×ULN), as the systemic crizotinib exposure was comparable to that from patients with normal hepatic function receiving the same crizotinib dose of 250 mg twice daily. The starting crizotinib dose for patients with moderate hepatic impairment (any AST and total bilirubin >1.5×ULN and ≤3×ULN) is recommended to be 200 mg twice daily, as the systemic crizotinib exposure increased compared to that from patients with normal hepatic function receiving the same dose of 200 mg twice daily, but was comparable to that from patients with normal hepatic function receiving 250 mg twice daily. The starting crizotinib dose for patients with severe hepatic impairment (any AST and total bilirubin >3×ULN) is recommended to be 250 mg once daily, as crizotinib doses greater than 250 mg once daily have not been studied in patients with severe hepatic impairment and may result in increases of systemic crizotinib exposure to supra-therapeutic levels.

Renal impairment:
No starting dose adjustment is needed for patients with mild (60 ≤ creatinine clearance [CL_{cr}] <90 mL/min) or moderate renal impairment (30 ≤ CL_{cr} <60 mL/min), since the population

pharmacokinetic analysis indicated no clinically meaningful changes in steady-state XALKORI exposure in these patients. XALKORI plasma concentrations may be increased in patients with severe renal impairment (CL_{cr} <30 mL/min). The XALKORI dose should be adjusted to 250 mg taken orally once daily in patients with severe renal impairment not requiring peritoneal dialysis or hemodialysis. The dose may be increased to 200 mg twice daily based on individual safety and tolerability after at least 4 weeks of treatment (see Sections **Special Warnings and Precautions for Use** and **Pharmacokinetic Properties**).

Pediatric patients:
The safety and efficacy of crizotinib in pediatric patients has not been established.

Elderly:
No starting dose adjustment is required (see Sections **Pharmacodynamic Properties** and **Pharmacokinetic Properties**).

Contraindications
Use of crizotinib is contraindicated in patients with hypersensitivity to crizotinib or to any of the excipients and severe hepatic impairment.

Special Warnings and Precautions for Use
Assessment of ALK and ROS1 status
When assessing either ALK or ROS1 status of a patient, it is important that a well-validated and robust methodology is chosen to avoid false negative or false positive determinations.

Hepatotoxicity
Drug-induced hepatotoxicity with fatal outcome occurred in 0.1% of 1722 patients treated with crizotinib across clinical trials. Concurrent elevations in ALT and/or AST ≥3×ULN and total bilirubin ≥2×ULN without significant elevations of alkaline phosphatase (≤2×ULN) have been observed in less than 1% of patients treated with crizotinib. Increases to Grade 3 or 4 ALT or AST elevations were observed in 187 (11%) and 95 (6%) of patients, respectively. Seventeen (1%) patients required permanent discontinuation from treatment associated with elevated transaminases, suggesting that these events were generally manageable by dosing modifications as defined in Table 2 (see Section **Posology and Method of Administration**). Transaminase elevations generally occurred within the first 2 months of treatment. Liver function tests including ALT, AST 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 elevations. For patients who develop transaminase elevations, see **Dose modification** section (see Section **Posology and Method of Administration**).

Interstitial lung Disease (Pneumonitis)
Crizotinib has been associated with severe, life-threatening, or fatal interstitial lung disease (ILD)/pneumonitis in clinical trials at a frequency of 26 (2%) of 1722 patients treated with crizotinib. These cases generally occurred within 3 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. Crizotinib should be permanently discontinued in patients diagnosed with treatment-related ILD/pneumonitis (see Section **Posology and Method of Administration**).

QT interval prolongation
QTc prolongation has been observed, which may lead to an increased risk for ventricular tachyarrhythmias (e.g., Torsade de-Pointes) or sudden death. The risk of QTc prolongation may be increased in patients concomitantly taking antiarrhythmics and in patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances (e.g., secondary to diarrhea or vomiting). XALKORI should be administered with caution to patients who have a history of or predisposition for QTc prolongation, or who are taking medicinal products that are known to prolong the QT interval. When using XALKORI in these patients, periodic monitoring with electrocardiograms and electrolytes should be considered. For patients who develop QTc prolongation, (see Sections **Posology and Method of Administration** and **Pharmacokinetic Properties)**.

Bradycardia
Bradycardia has been reported in clinical studies, and it was usually asymptomatic. The full effect of crizotinib on pulse rate may not develop until several weeks after start of treatment. 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 (syncope, dizziness, hypotension). Monthly monitoring of pulse rate and blood pressure is recommended. Dose modification is not required in cases of asymptomatic bradycardia. In cases of symptomatic bradycardia, crizotinib should be held and the use of concomitant medications should be re-evaluated. For management of patients who develop symptomatic bradycardia, see Dose modification and Undesirable Effects sections (see Sections **Posology and Method of Administration** and **Undesirable Effects**).

Cardiac failure
In clinical studies with crizotinib and during post-marketing surveillance in adult patients, severe, life-threatening, or fatal adverse reactions of cardiac failure were reported.

Patients with or without pre-existing cardiac disorders, receiving crizotinib, should be monitored for signs and symptoms of heart failure (dyspnoea, oedema, rapid weight gain from fluid retention). Dosing interruption, dose reduction, or discontinuation should be considered as appropriate if such symptoms are observed.

Neutropenia and leukopenia
In clinical studies with crizotinib in adult patients with either ALK-positive or ROS1-positive NSCLC, Grade 3 or 4 neutropenia has been very commonly reported (12%). Less than 0.5% of adult patients with either ALK-positive or ROS1-positive NSCLC experienced febrile neutropenia in clinical studies with crizotinib. 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.

Gastrointestinal perforation
In clinical studies with crizotinib, events of gastrointestinal perforations were reported. There were reports of fatal cases of gastrointestinal perforation during post-marketing use of crizotinib.

Crizotinib should be used with caution in patients at risk for gastrointestinal perforation (e.g., history of diverticulitis, metastases to the gastrointestinal tract, concomitant use of medicinal products with a recognised risk of gastrointestinal perforation).

Crizotinib should be discontinued in patients who develop gastrointestinal perforation. Patients should be informed of the first signs of gastrointestinal perforations and be advised to consult rapidly in case of occurrence.

Renal effects
Blood creatinine increase and creatinine clearance decreased were observed in patients in clinical studies with crizotinib. Renal failure and acute renal failure were reported in patients treated with crizotinib in clinical studies and during post-marketing. Cases with fatal outcome, cases requiring haemodialysis and cases of Grade 4 hyperkalaemia were also observed in adult patients. Monitoring of patients for renal function at baseline and during therapy with crizotinib is recommended, with particular attention to those who have risk factors or previous history of renal impairment.

Renal impairment
If patients have severe renal impairment not requiring peritoneal dialysis or hemodialysis, the dose of crizotinib should be adjusted (see Sections **Posology and Method of Administration** and **Pharmacokinetic Properties**).

Visual effects
Vision disorder occurred in patients in Study 1001 and Study 1005. Ophthalmological evaluation should be considered if vision disorder persists or worsens in severity.

Photosensitivity
Photosensitivity has been reported in patients treated with Xalkori. Patients should be advised to avoid prolonged sun exposure while taking Xalkori and, when outdoors, to take protective measures (e.g., use of protective clothing and/or sunscreen).

Non-adenocarcinoma histology
Limited information is available in patients with ALK-positive and ROS1-positive NSCLC with non-adenocarcinoma histology, including squamous cell carcinoma (SCC).

Dietary sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per 200 mg or 250 mg capsule, that is to say essentially 'sodium-free'.

Interaction with Other Medicinal Products and Other Forms of Interaction

Crizotinib is a substrate of CYP3A4/5 and also a moderate inhibitor of CYP3A. *In vitro* studies in human liver microsomes demonstrated that crizotinib is a time-dependent inhibitor of CYP3A.

Agents that may increase crizotinib plasma concentrations

Co-administration of crizotinib with strong CYP3A inhibitors may increase crizotinib plasma concentrations (see Section **Pharmacokinetic Properties**). Co-administration of a single 150 mg oral dose of crizotinib in the presence of ketoconazole (200 mg twice daily), a strong CYP3A inhibitor, resulted in increases in crizotinib systemic exposure, with crizotinib AUC_{inf} and C_{max} values that were approximately 3.2-fold and 1.4-fold, respectively, those seen when crizotinib was administered alone.

Therefore, the concomitant use of strong CYP3A inhibitors (certain protease inhibitors like atazanavir, indinavir, nelfinavir, ritonavir, saquinavir, and, certain azole antifungals like itraconazole, ketoconazole, and voriconazole, certain macrolides like clarithromycin, telithromycin, and troleandomycin) should be avoided. Grapefruit or grapefruit juice may also increase plasma concentrations of crizotinib and should be avoided (see Sections **Posology and Method of Administration** and **Special Warnings and Precautions for Use**). Furthermore, the effect of CYP3A inhibitors on steady-state crizotinib exposure has not been established.

Agents that may decrease crizotinib plasma concentrations

Co-administration of a single 250 mg crizotinib dose with rifampicin (600 mg QD), a strong CYP3A4 inducer, resulted in 82% and 69% decreases in crizotinib AUC_{inf} and C_{max}, respectively, compared to when crizotinib was given alone. Co-administration of crizotinib with strong CYP3A inducers may decrease crizotinib plasma concentrations (see Section **Pharmacokinetic Properties**). 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 Section **Special Warnings and Precautions for Use**). Furthermore, the effect of CYP3A inducers on steady-state crizotinib exposure has not been established.

Agents whose plasma concentrations may be altered by crizotinib

Following 28 days of crizotinib dosing at 250 mg taken twice daily in cancer patients, the oral midazolam AUC was 3.7-fold those seen when midazolam was administered alone, suggesting that crizotinib is a moderate inhibitor of CYP3A. Therefore, co-administration of crizotinib with CYP3A substrates with narrow therapeutic indices, including but not limited to alfentanil, cisapride, cyclosporine, ergot derivatives, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus should be avoided (see Section **Special Warnings and**

Precautions for Use). If the combination is needed, then close clinical monitoring should be exercised.

An *in vitro* study in human hepatocytes indicated that crizotinib may induce pregnane X receptor (PXR)-regulated enzymes (e.g., CYP2B6, CYP2C8, CYP2C9, UGT1A1, with the exception of CYP3A4). Therefore, caution should be exercised in administering crizotinib in combination with medicinal products that are predominantly metabolized by these enzymes. Of note, the effectiveness of concomitant administration of oral contraceptives may be altered.

The inhibitory effect of crizotinib on UGTs, notably UGT1A1, is not established. Therefore, caution should be exercised when crizotinib and substrates of UGTs, such as paracetamol, morphine, or irinotecan, are combined.

Based on an *in vitro* study, crizotinib is predicted to inhibit intestinal P-gp. Therefore, administration of crizotinib with medicinal products that are substrates of P-gp (e.g., digoxin, dabigatran, colchicine, pravastatin) may increase their therapeutic effect and adverse reactions. Close clinical surveillance is recommended when crizotinib is administered with these medicinal products.

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

Fertility, Pregnancy and Lactation
Contraception in males and females
Women of child-bearing 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.

Pregnancy
XALKORI may cause fetal harm when administered to a pregnant woman. Studies in animals have shown reproductive toxicity. 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 area under the plasma concentration-time curve [AUC]).

There are no data in pregnant women using crizotinib. This medicinal product should not be used during pregnancy unless the clinical condition of the mother requires treatment. Pregnant women, or patients becoming pregnant while receiving crizotinib, or treated male

patients as partners of pregnant women, should be apprised of the potential hazard to the foetus.

Breast-feeding
It is not known whether crizotinib and its metabolites are excreted in human milk. Because of the potential harm to the infant, mothers should be advised to avoid breast-feeding while receiving XALKORI.

Fertility
Based on nonclinical safety findings, male and female fertility may be compromised by treatment with XALKORI. Both men and women should seek advice for fertility preservation before treatment.

Effects on Ability to Drive and Use Machines
No studies on the effect of crizotinib on the ability to drive and use machines have been performed. However, caution should be exercised when driving or operating machinery by patients who experience vision disorder, dizziness, or fatigue while taking crizotinib (see Section **Undesirable Effects**).

Undesirable Effects
Summary of the safety profile
The data described below reflect exposure to crizotinib in 1669 patients with ALK-positive advanced NSCLC who participated in randomized Phase 3 Studies 1007 or 1014 or in single-arm Studies 1001 or 1005, and in 53 patients with ROS1-positive advanced NSCLC who participated in single-arm Study 1001, for a total of 1722 patients (see Section **Pharmacodynamic Properties**). These patients received a starting oral dose of 250 mg twice daily continuously. In Study 1014, the median duration of study treatment was 47 weeks for patients in the crizotinib arm (N=171); the median duration of treatment was 23 weeks for patients who crossed over from the chemotherapy arm to receive crizotinib treatment (N=109). In Study 1007, the median duration of study treatment was 48 weeks for patients in the crizotinib arm (N=172). For ALK-positive NSCLC patients in Studies 1001 (N=154) and 1005 (N=1063), the median duration of treatment was 57 and 45 weeks, respectively. For ROS1 positive NSCLC patients in Study 1001 (N=53), the median duration of treatment was 101 weeks.

The most serious adverse reactions in 1722 patients with either ALK-positive or ROS1-positive advanced NSCLC were hepatotoxicity, ILD/pneumonitis, neutropenia, and QT interval prolongation (see Section **Special Warnings and Precautions for Use**). The most common adverse reactions (≥25%) in patients with either ALK-positive or ROS1-positive NSCLC were vision disorder, nausea, diarrhea, vomiting, edema, constipation, elevated transaminases, fatigue, decreased appetite, dizziness, and neuropathy.

In 1722 patients with either ALK-positive or ROS1-positive NSCLC treated with crizotinib, all-causality adverse events associated with dosing interruptions or dose reductions occurred

in 763 (44%) and 259 (15%) patients, respectively. All-causality adverse events associated with permanent treatment discontinuation occurred in 302 (18%) patients.

Table 3. ADRs by SOC and CIOMS frequency category listed in order of decreasing medical seriousness or clinical importance within each frequency category and SOC (Pooled ROS1-Positive NSCLC and ALK-Positive NSCLC; n=1722).*

It presents adverse drug reactions experienced by ALK-positive NSCLC patients who participated in randomized Phase 3 Studies 1007 or 1014 or in single-arm Studies 1001 or 1005 (N=1669), and in ROS1-positive NSCLC patients who participated in single-arm Study 1001 (N=53), for a total dataset of 1722 patients (see Section **Pharmacodynamic Properties**). Adverse drug reactions are listed in order of decreasing medical seriousness or clinical importance within each frequency category and SOC.*

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1000 to <1/100
Blood and lymphatic system disorders	Neutropenia[a] Leukopenia[b]		
Metabolism and nutrition disorders	Decreased appetite		
Nervous system disorders	Neuropathy[c] Dizziness[d] Dysgeusia		
Eye disorders	Vision disorder[e]		
Cardiac disorders	Bradycardia[f]	Electrocardiogram QT prolonged Syncope	
Respiratory, thoracic and mediastinal disorders		Interstitial lung disease[g]	
Gastrointestinal disorders	Vomiting Diarrhoea Nausea Constipation	Oesophagitis[h] Dyspepsia	
Hepatobiliary disorders	Elevated transaminases[i]	Blood alkaline phosphatase increased	Hepatic failure
Skin and subcutaneous tissue disorders	Rash		
Renal and urinary disorders		Renal cyst[j] Blood creatinine increased[k]	
General disorders and administration site conditions	Oedema[l] Fatigue		

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1000 to <1/100
Investigations		Blood testosterone decreased[m]	Blood creatine phosphokinase increased(<1%)**

* The frequency categories of adverse drug reactions were based on the data cutoff date of 30 Nov 2013 for patients with ALK positive NSCLC, and based on the data cutoff date of 30 Nov 2014 for patients with ROS1-positive NSCLC.

** Creatine phosphokinase was not a standard laboratory test in the crizotinib clinical trials.

Event terms that represent the same medical concept or condition were grouped together and reported as a single adverse drug reaction in the table above. Terms actually reported in the studies up to the data cutoff date and contributing to the relevant adverse drug reaction are indicated in parentheses, as listed below.

a. Neutropenia (Febrile neutropenia, Neutropenia, Neutrophil count decreased).
b. Leukopenia (Leukopenia, White blood cell count decreased).
c. Neuropathy (Burning sensation, Dysaesthesia, Formication, Gait disturbance, Hyperaesthesia, Hypoaesthesia, Hypotonia, Motor dysfunction, Muscle atrophy, Muscular weakness, Neuralgia, Neuritis, Neuropathy peripheral, Neurotoxicity, Paraesthesia, Peripheral motor neuropathy, Peripheral sensorimotor neuropathy, Peripheral sensory neuropathy, Peroneal nerve palsy, Polyneuropathy, Sensory disturbance, Skin burning sensation).
d. Dizziness (Balance disorder, Dizziness, Dizziness postural, Presyncope).
e. Vision disorder (Diplopia, Halo vision, Photophobia, Photopsia, Vision blurred, Visual acuity reduced, Visual brightness, Visual impairment, Visual perseveration, Vitreous floaters).
f. Bradycardia (Bradycardia, Heart rate decreased, Sinus bradycardia).
g. Interstitial lung disease (Acute respiratory distress syndrome, Alveolitis, Interstitial lung disease, Pneumonitis).
h. Oesophagitis (Oesophagitis, Oesophageal ulcer).
i. Elevated transaminases (Alanine aminotransferase increased, Aspartate aminotransferase increased, Gamma-glutamyltransferase increased, Hepatic enzyme increased, Hepatic function abnormal, Liver function test abnormal, Transaminases increased).
j. Renal cyst (Renal abscess, Renal cyst, Renal cyst haemorrhage, Renal cyst infection).
k. Blood creatinine increased (Blood creatinine increased, Creatinine renal clearance decreased).
l. Oedema (Face oedema, Generalised oedema, Local swelling, Localised oedema, Oedema, Oedema peripheral, Periorbital oedema).
m. Blood testosterone decreased (Blood testosterone decreased, Hypogonadism, Secondary hypogonadism).

Description of selected adverse reactions

Visual Effects

In clinical trials of patients with either ALK-positive or ROS1-positive advanced NSCLC, all-causality vision disorder, most commonly visual impairment, photopsia, vision blurred, and vitreous floaters, was experienced by 1084 (63%) of 1722 patients treated with crizotinib. Of the 1084 patients who experienced vision disorder, 95% patients had events that were mild in severity. Ophthalmological evaluation should be considered if vision disorder persists or worsens in severity. Seven (0.4%) patients had temporary treatment discontinuation and 2 (0.1%) patients had a dose reduction associated with vision disorder. There were no permanent discontinuations associated with vision disorder for any of the 1722 patients treated with crizotinib.

Based on the Visual Symptom Assessment Questionnaire (VSAQ-ALK), patients treated with crizotinib in Study 1007 and Study 1014 reported a higher incidence of visual disturbances compared to patients treated with chemotherapy. The onset of vision disorder generally occurred during the first week of drug administration. The majority of patients in

the crizotinib arms in Study 1007 and Study 1014 (>50%) reported visual disturbances, which occurred at a frequency of 4 to 7 days each week, lasted up to 1 minute, and had mild or no impact (scores 0 to 3 out of a maximum score of 10) on daily activities as captured by the VSAQ-ALK questionnaire.

Gastrointestinal Effects
Nausea (57%), diarrhea (54%), vomiting (51%), and constipation (43%) were the most commonly reported all-causality gastrointestinal events. Most events were mild to moderate in severity. Median times to onset for nausea and vomiting were 3 days, and these events declined in frequency after 3 weeks of treatment. Supportive care should include the use of antiemetic medications. In clinical trials, the most commonly used antiemetic medications were ondansetron and prochlorperazine. Median times to onset for diarrhea and constipation were 13 and 17 days, respectively. Supportive care for diarrhea and constipation should include the use of standard antidiarrheal and laxative medications, respectively.

Nervous System Effects
All-causality neuropathy, as defined in Table 3, was experienced by 435 (25%) of 1722 patients treated with crizotinib, and was primarily Grade 1 or 2 in severity. Dizziness and dysgeusia were also very commonly reported and were primarily Grade 1 in severity.

Bradycardia
In clinical trials of patients with either ALK-positive or ROS1-positive advanced NSCLC, all-causality bradycardia was experienced by 219 (13%) of 1722 patients treated with crizotinib. Most events were mild in severity. A total of 259 (16%) of 1666 patients with at least 1 postbaseline vital sign assessment had a pulse rate <50 bpm. The use of concomitant medications associated with bradycardia should be carefully evaluated. Patients who develop symptomatic bradycardia should be managed as recommended in the Dose Modification and Warnings and Precautions sections (see Sections **Posology and Method of Administration** and **Special Warnings and Precautions for Use**).

Renal Cyst
All-causality complex renal cysts were experienced by 52 (3%) of 1722 patients treated with crizotinib. There were no reports of clinically relevant abnormal urinalyses or renal impairment in these cases, although local cystic invasion beyond the kidney was observed in some patients. Periodic monitoring with imaging and urinalysis should be considered in patients who develop renal cysts.

Laboratory Abnormalities/Testing
Hematologic Laboratory Abnormalities
In clinical studies of crizotinib in patients with either ALK positive or ROS1 positive advanced NSCLC, shifts to Grade 3 or 4 decreases in leukocytes and neutrophils were observed in 64 (4%) and 226 (13%) patients, 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. For patients who develop hematologic laboratory abnormalities, see **Dose modification** section (see Section **Posology and Method of Administration)**.

Hepatic Laboratory Abnormalities
In clinical studies of crizotinib in patients with either ALK positive or ROS1 positive advanced NSCLC, shifts to Grade 3 or 4 ALT, AST, and alkaline phosphatase were observed in 187 (11%), 95 (6%), and 33 (2%) patients, respectively. Patients should be monitored for hepatotoxicity and managed as recommended in Warnings and Precautions section (see Section **Special Warnings and Precautions for Use**).

Renal Laboratory Abnormalities
In clinical studies of crizotinib in patients with ALK-positive advanced NSCLC, the estimated glomerular filtration rate (eGFR) decreased from a baseline median of 96.42 mL/min/1.73 m^2 (n=1681) to a median of 80.23 mL/min/1.73 m^2 at 2 weeks of treatment (n=1499). Median eGFR appeared to be relatively stable from 12 weeks of treatment (78.06 mL/min/1.73 m^2, n=1338) through 104 weeks of treatment (75.45 mL/min/1.73 m^2, n=315) and increased to 83.02 mL/min/1.73 m^2 at 28 days after the last dose of crizotinib (n=123).

Shifts to eGFR Grade 4 (15 to <30 mL/min/1.73 m^2) or to eGFR Grade 5 (<15 mL/min/1.73 m^2) were observed in 3% and <1% of patients, respectively.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:
Pusat Farmakovigilans/MESO Nasional
Direktorat Pengawasan Keamanan, Mutu, dan Ekspor lmpor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif
Badan Pengawas Obat dan Makanan
JI. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Phone: +62-21-4244691 Ext .1079
Website: https://e-meso.pom.go.id/ADR

Overdose
Treatment of overdose with crizotinib should consist of general supportive measures. There is no antidote for crizotinib.

PHARMACOLOGICAL PROPERTIES
Pharmacotherapeutic group: Anti-neoplastic agents, protein kinase inhibitor; ATC code: L01XE16.

Pharmacodynamic Properties
Crizotinib is a selective small-molecule inhibitor of the 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 ROS1 (c-ros), and Recepteur d'Origine Nantais (RON) RTKs. Crizotinib demonstrated concentration-dependent inhibition of the kinase activity of ALK, ROS1, and c-Met in biochemical assays and inhibited phosphorylation and modulated 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 (including echinoderm microtubule-associated protein-like 4 [EML4]-ALK and nucleophosmin [NPM]-ALK), 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 fusion proteins. The antitumor efficacy of crizotinib was dose-dependent and correlated to pharmacodynamic inhibition of phosphorylation of ALK fusion proteins (including EML4-ALK and NPM-ALK) in tumors *in vivo*. Crizotinib also demonstrated marked antitumor activity in mouse xenograft studies, where tumors were generated using a panel of NIH-3T3 cell lines engineered to express key ROS1 fusions identified in human tumors. The antitumor efficacy of crizotinib was dose-dependent and demonstrated a correlation with inhibition of ROS1 phosphorylation *in vivo*.

Pediatric population
The safety and efficacy of crizotinib in pediatric patients has not been established. Decreased bone formation in growing long bones was observed in immature rats at 150 mg/kg/day following once daily dosing for 28 days (approximately 3 times human clinical exposure based on AUC). Other toxicities of potential concern to pediatric patients have not been evaluated in juvenile animals.

Clinical studies
Previously Untreated ALK-Positive Advanced NSCLC – Randomized Phase 3 Study 1014
The use of single-agent crizotinib for the first-line treatment of ALK-positive advanced NSCLC in patients with or without brain metastases was investigated in a multicenter, multinational, randomized, open-label Phase 3 Study 1014. The primary objective of this study was to demonstrate that crizotinib was superior to first-line standard-of-care platinum-based chemotherapy (pemetrexed-cisplatin or pemetrexed-carboplatin) in prolonging Progression-Free Survival (PFS) as assessed by independent radiology review (IRR) in patients with ALK-positive advanced NSCLC who had not received previous systemic treatment for advanced disease. Secondary objectives were to compare measures of clinical efficacy including Objective Response Rate (ORR) as assessed by IRR, Duration of Response (DR), Overall Survival (OS), Intracranial Time to Progression (IC-TTP) as assessed by IRR, and Patient-Reported Outcomes (PRO).

The full analysis population for Study 1014 included 343 patients with ALK-positive advanced NSCLC as identified by Fluorescence In Situ Hybridization (FISH) prior to randomization. One hundred seventy-two (172) patients were randomized to the crizotinib arm (171 patients received crizotinib 250 mg orally twice daily) and 171 patients were randomized to the chemotherapy arm (169 patients received chemotherapy; 91 patients were treated with pemetrexed/cisplatin and 78 patients were treated with pemetrexed/carboplatin). Chemotherapy consisted of pemetrexed 500 mg/m^2 in combination with cisplatin 75 mg/m^2 or carboplatin at a dose calculated to produce an AUC of 5 or 6 mg • min/mL. Chemotherapy was given by intravenous infusion every 3 weeks for up to 6 cycles. The median duration of study treatment was 47 weeks in the crizotinib arm and 18 weeks in the chemotherapy arm. Patients could continue crizotinib treatment beyond the time of Response Evaluation Criteria in Solid Tumors (RECIST)-defined disease progression, as assessed by IRR, at the discretion of the investigator if the patient was still experiencing clinical benefit. Patients in the chemotherapy arm who completed 6 cycles were to continue in the study without further treatment, but have ongoing tumor assessments until RECIST-defined disease progression as determined by IRR. Patients in the chemotherapy arm who had RECIST-defined progression of disease as assessed by IRR had the option to receive crizotinib. One hundred forty-four (84%) patients received crizotinib after the randomization phase (128 patients through the crossover process and 16 patients as follow-up therapy).

Randomization was stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0-1 vs. 2), race (Asian vs. non-Asian), and brain metastases (present vs. absent).

Baseline demographic and disease characteristics were similar between the crizotinib and chemotherapy treatment arms with regard to gender (female: 61% vs. 63% for crizotinib vs. chemotherapy, respectively), median age (52 years vs. 54 years), race (White: 53% vs. 50%, and Asian: 45% vs. 47%); smoking status (current smokers: 6% vs. 3%, former smokers: 33% vs. 32%, and never smokers: 62% vs. 65%), metastatic disease (98% in both treatment arms), tumor histology (adenocarcinoma: 92% vs. 93%), performance status (ECOG 0 or 1: 94% vs. 95%, and ECOG 2: 6% vs. 5%), and brain metastases (present 26% vs. 28%).

Crizotinib significantly prolonged PFS compared to chemotherapy as assessed by IRR. There was a numerical improvement in OS in the patients treated with crizotinib, although this improvement was not statistically significant. Efficacy data from randomized Phase 3 Study 1014 are summarized in Table 4, and the Kaplan-Meier curves for PFS and OS are shown in Figures 1 and 2, respectively.

Table 4. Efficacy Results From Randomized Phase 3 Study 1014 (Full Analysis Population) in Patients With Previously Untreated ALK-Positive Advanced NSCLC

Response Parameter	Crizotinib (N=172)	Chemotherapy (N=171)
Progression-Free Survival (Based on IRR)		

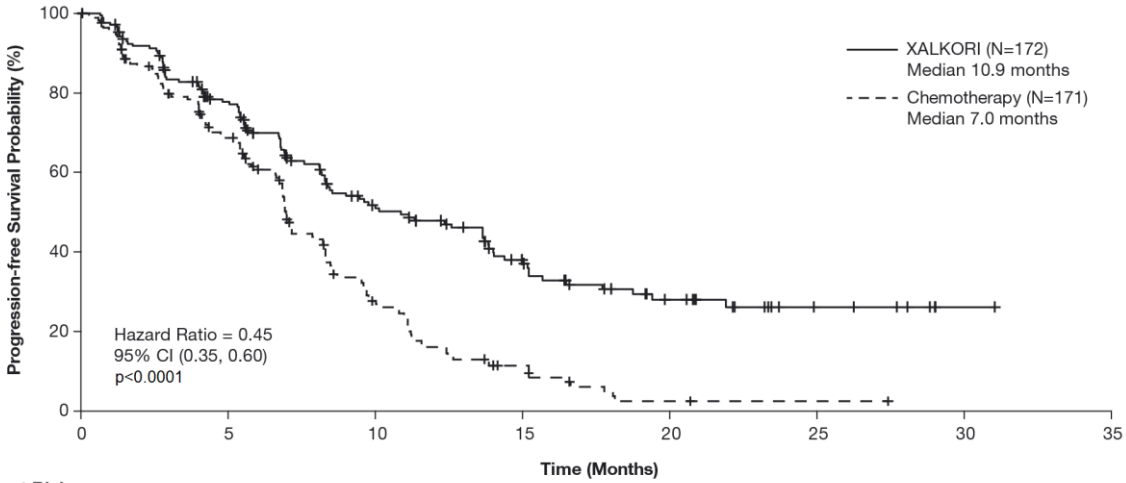
Number with event, n (%)	100 (58%)	137 (80%)
Median PFS in months (95% CI)	10.9 (8.3, 13.9)	7.0[a] (6.8, 8.2)
HR (95% CI)[b]	0.45 (0.35, 0.60)	
p-value[c]	<0.0001	
Overall Survival[d]		
Number of deaths, n (%)	71 (41%)	81 (47%)
Median OS in months (95% CI)	NR (45.8, NR)	47.5 (32.2, NR)
HR (95% CI)[b]	0.76 (0.55, 1.05)	
p-value[c]	0.0489	
12-Month survival probability,[d] % (95% CI)	83.5 (77.0, 88.3)	78.4 (71.3, 83.9)
18-Month survival probability,[d] % (95% CI)	71.5 (64.0, 77.7)	66.6 (58.8, 73.2)
48-Month survival probability,[d] % (95% CI)	56.6 (48.3, 64.1)	49.1 (40.5, 57.1)
Objective Response Rate (based on IRR)		
Objective Response Rate % (95% CI)	74% (67, 81)	45%[e] (37, 53)
p-value[f]	<0.0001	
Duration of Response		
Months[g] (95% CI)	11.3 (8.1, 13.8)	5.3 (4.1, 5.8)

Abbreviations: N/n=number of patients; CI=confidence interval; HR=hazard ratio; IRR=independent radiology review; NR=not reached; PFS=progression-free survival; OS=overall survival.

* PFS, Objective Response Rate and Duration of Response are based on the data cutoff date of 30 November 2013; OS is based on the last patient last visit date of 30 November 2016, and represents a median follow up of approximately 46 months.

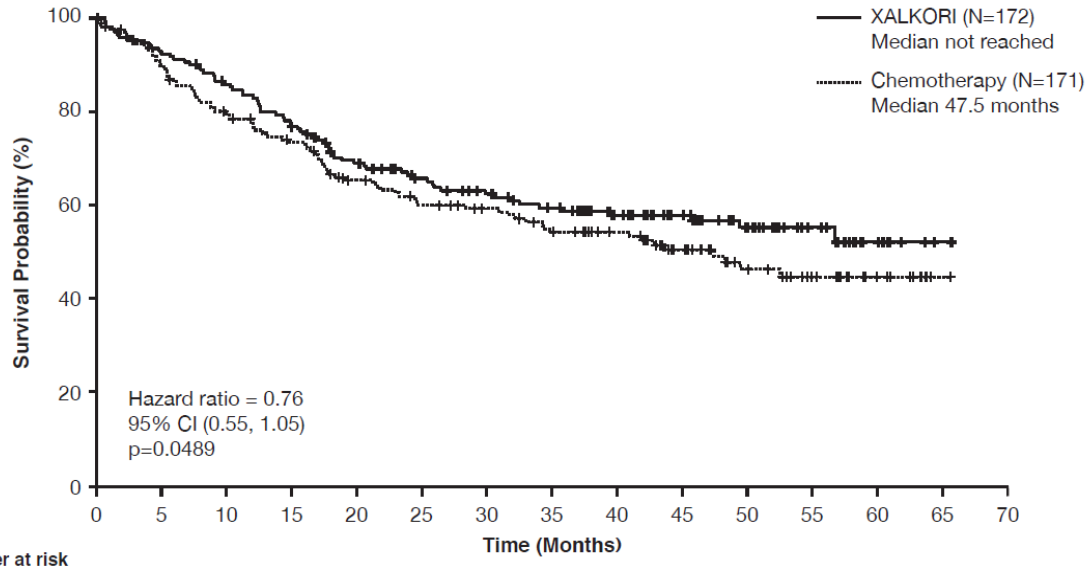
a. Median PFS times were 6.9 months (95% CI: 6.6, 8.3) for pemetrexed/cisplatin (HR=0.49; p-value <0.0001 for crizotinib compared with pemetrexed/cisplatin) and 7.0 months (95% CI: 5.9, 8.3) for pemetrexed/carboplatin (HR=0.45; p-value <0.0001 for crizotinib compared with pemetrexed/carboplatin).
b. Based on the Cox proportional hazards stratified analysis.
c. Based on the stratified log-rank test (1-sided).
d. Updated based on final OS analysis. OS analysis was not adjusted for the potentially confounding effects of cross over (144 [84%] patients in the chemotherapy arm received subsequent crizotinib treatment).
e. ORRs were 47% (95% CI: 37, 58) for pemetrexed/cisplatin (p-value <0.0001 compared with crizotinib) and 44% (95% CI: 32, 55) for pemetrexed/carboplatin (p-value <0.0001 compared with crizotinib).
f. Based on the stratified Cochran-Mantel-Haenszel test (2-sided).
g. Estimated using the Kaplan-Meier method.

Figure 1. Kaplan-Meier Curves for Progression-Free Survival (Based on IRR) by Treatment Arm in Randomized Phase 3 Study 1014 (Full Analysis Population) in Patients With Previously Untreated ALK-Positive Advanced NSCLC



Number at Risk								
XALKORI	172	120	65	38	19	7	1	0
Chemotherapy	171	105	36	12	2	1	0	0

Figure 2. Kaplan-Meier Curves for Overall Survival by Treatment Arm in Randomized Phase 3 Study 1014 (Full Analysis Population) in Patients With Previously Untreated ALK-Positive Advanced NSCLC



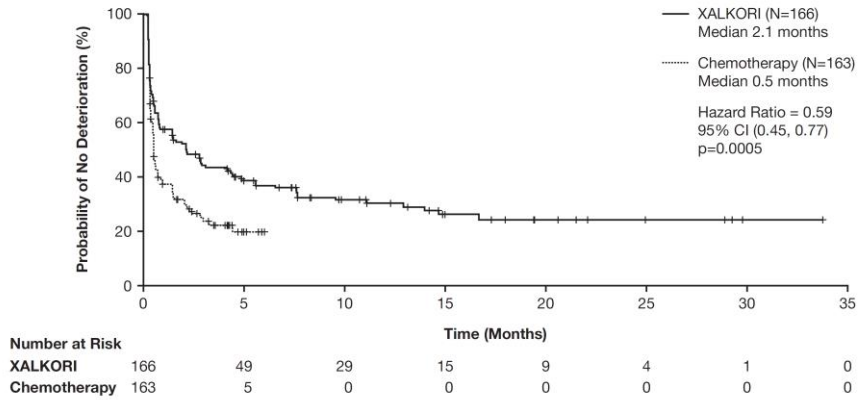
Number at risk														
XALKORI	172	157	144	128	111	98	89	79	65	51	36	20	8	1	0
Chemotherapy	171	150	131	118	100	89	82	73	63	46	31	21	11	1	0

Based on IRR assessment, a total of 9 (23.1%) of the 39 patients in the crizotinib arm and 12 (30.0%) of the 40 patients in the chemotherapy arm with previously treated baseline brain metastases experienced progression of intracranial lesions or developed new intracranial lesions. For patients with previously treated baseline brain metastases, the median intracranial TTP (IC-TTP) was 15.7 months in the crizotinib arm and 12.5 months in the chemotherapy arm (HR=0.45 [95% CI: 0.19, 1.07]; 1-sided p-value=0.0315). A total of 16 (12.1%) of the 132 patients in the crizotinib arm and 14 (10.7%) of the 131 patients in the chemotherapy arm without baseline brain metastases developed new intracranial lesions. For patients without baseline brain metastases, the median IC-TTP was not reached in either the crizotinib or the chemotherapy arms (HR=0.69 [95% CI: 0.33, 1.45]; 1-sided p-value=0.1617).

Patient-reported symptoms and global QOL was collected using the EORTC QLQ-C30 and its lung cancer module (EORTC QLQ-LC13) at baseline (Day 1), Day 7 and Day 15 of Cycle 1, and Day 1 of each subsequent treatment cycle. A total of 166 patients in the crizotinib arm and 163 patients in the chemotherapy arm had completed the EORTC QLQ-C30 and LC-13 questionnaires at baseline and at least 1 postbaseline visit.

Time to Deterioration (TTD) was prespecified as the time from randomization to the first occurrence of a ≥10-point increase in scores from baseline in symptoms of pain (EORTC QLQ-LC13 pain in chest), cough (EORTC QLQ-LC13 cough), or dyspnea (EORTC QLQ-LC13 dyspnea). The median TTD in patient-reported pain in chest, dyspnea, or cough as a composite endpoint was 2.1 months (95% CI: 0.8 months, 4.2 months) in the crizotinib arm compared to 0.5 months (95% CI: 0.4 months, 0.7 months) in the chemotherapy arm. Treatment with crizotinib was associated with a significantly longer TTD in the symptoms of pain in chest, dyspnea, or cough compared to chemotherapy (hazard ratio 0.59; 95% CI: 0.45, 0.77; Hochberg-adjusted log-rank 2-sided p-value=0.0005).

Figure 3. Kaplan-Meier Plot of Time to Deterioration in Pain (in Chest), Dyspnea, or Cough (Composite Endpoint) by Treatment Arm (Patient-Reported Outcome Evaluable Population) in Patients With Previously Untreated ALK-Positive Advanced NSCLC



The change from baseline scores was found to be significantly different between the 2 treatment arms, with a significantly greater improvement observed in global quality of life in the crizotinib arm compared to the chemotherapy arm (overall difference in change from baseline scores 13.8; p-value <0.0001).

Previously Treated ALK-Positive Advanced NSCLC – Randomized Phase 3 Study 1007
The use of single-agent crizotinib in the treatment of ALK-positive advanced NSCLC with or without brain metastases was investigated in a multicenter, multinational, randomized, open-label Phase 3 study (Study 1007). The primary objective of this study was to demonstrate that crizotinib 250 mg orally twice daily was superior to standard-of-care chemotherapy (pemetrexed 500 mg/m^2 or docetaxel 75 mg/m^2) intravenously (IV) every 21 days in prolonging Progression-free Survival (PFS) 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 crizotinib in Study 1005 upon RECIST-defined disease progression confirmed by independent radiology review (IRR). The primary efficacy endpoint was PFS with disease progression events determined by IRR. Secondary endpoints included ORR as determined by IRR, DR, OS, and PRO. The full analysis population for Study 1007 included 347 patients with ALK-positive advanced NSCLC. One hundred seventy-three (173) patients were randomized to the crizotinib arm (172 patients received crizotinib) 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 crizotinib 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. Fifty eight of 84 (69%) patients treated with crizotinib and 17 of 119 (14%) patients treated with chemotherapy continued treatment for at least 3 weeks after objective disease progression.

Baseline demographic and disease characteristics for patients in this study were similar between the crizotinib and chemotherapy arms with regard to gender (female: 57% vs. 55% for crizotinib vs. chemotherapy, respectively), median age (51 years vs. 49 years), race (White: 52% in both treatment arms, and Asian: 46% vs. 45%), smoking status (current smokers: 3% vs. 5%, former smokers: 34% vs. 31%, and never smokers: 62% vs. 64%), metastatic disease (95% vs. 91%), tumor histology (adenocarcinoma: 94% vs. 92%), performance status (ECOG 0 or 1: 89% vs. 91%, ECOG 2: 11% vs. 9%), and brain metastases (present: 35% in both treatment arms).

Crizotinib significantly prolonged PFS compared to chemotherapy as assessed by IRR. Efficacy data from randomized Phase 3 Study 1007 are summarized in Table 5, and the Kaplan-Meier curve for PFS is shown in Figure 4.

Table 5. Efficacy Results From Randomized Phase 3 Study 1007 (Full Analysis Population) in Patients With Previously Treated ALK-Positive Advanced NSCLC *

Response Parameter	Crizotinib (N=173)	Chemotherapy (N=174)
Progression-Free Survival (Based on IRR)		
Number with event, n (%)	100 (58%)	127 (73%)
Median PFS in months (95% CI)	7.7 (6.0, 8.8)	3.0[a] (2.6, 4.3)
HR (95% CI)[b]	0.49 (0.37, 0.64)	
p-value[c]	<0.0001	
Overall Survival[d]		
Number of deaths, n (%)	116 (67%)	126 (72%)
Median OS in months (95% CI)	21.7 (18.9, 30.5)	21.9 (16.8, 26.0)
HR (95% CI)[b]	0.85 (0.66, 1.10)	
p-value[c]	0.1145	
Objective Response Rate (based on IRR)		
Objective Response Rate % (95% CI)	65% (58, 72)	20%[e] (14, 26)
p-value[f]	<0.0001	
Duration of Response		
Median[g], months (95% CI)	7.4 (6.1, 9.7)	5.6 (3.4, 8.3)

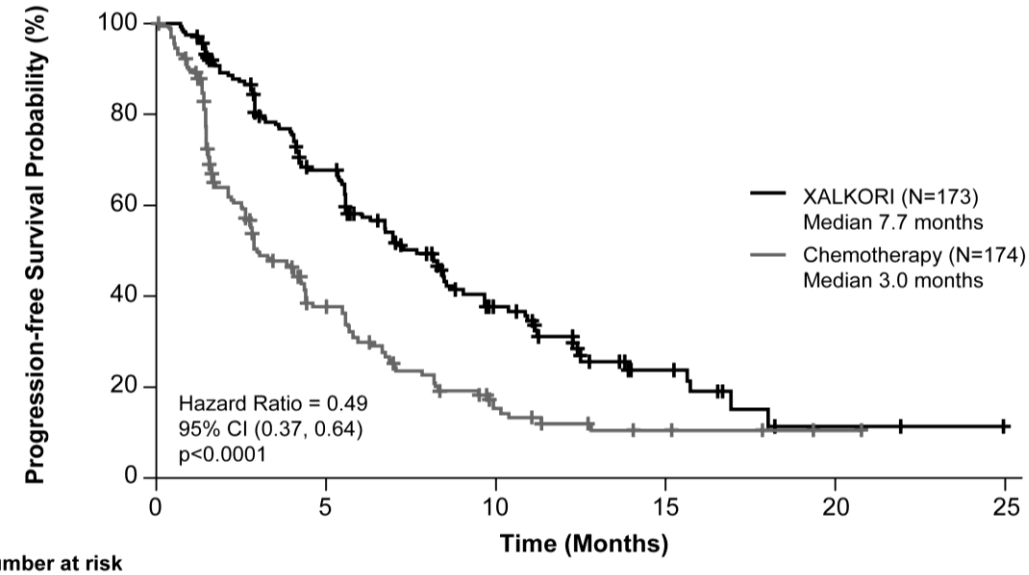
Abbreviations: N/n=number of patients; CI=confidence interval; HR=hazard ratio; IRR=independent radiology review; PFS=progression-free survival; OS=overall survival.

* PFS, Objective Response Rate and Duration of Response are based on the data cutoff date of 30 March 2012; OS is based on the data cutoff date of 31 August 2015.

a. Median PFS times were 4.2 months (95% CI: 2.8, 5.7) for pemetrexed (HR=0.59; p-value=0.0004 for XALKORI compared with pemetrexed) and 2.6 months (95% CI: 1.6, 4.0) for docetaxel (HR=0.30; p-value <0.0001 for XALKORI compared with docetaxel).
b. Based on the Cox proportional hazards stratified analysis.
c. Based on the stratified log-rank test (1-sided).
d. Updated based on final OS analysis. OS analysis was not adjusted for the potentially confounding effects of cross over.
e. ORRs were 29% (95% CI: 21, 39) for pemetrexed (p-value <0.0001 compared with XALKORI) and 7% (95% CI: 2, 16) for docetaxel (p-value <0.0001 compared with XALKORI).
f. Based on the stratified Cochran-Mantel-Haenszel test (2-sided).
g. Estimated using the Kaplan-Meier method.

Figure 4. Kaplan-Meier Curves for Progression-Free Survival (Based on IRR) by Treatment Arm in Randomized Phase 3 Study 1007 (Full Analysis

Population) in Patients With Previously Treated ALK-Positive Advanced NSCLC



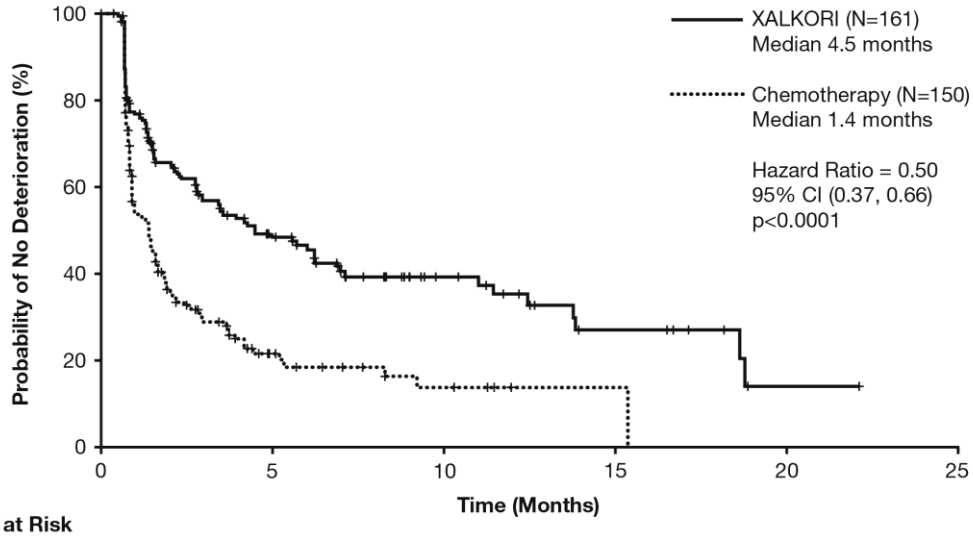
Number at risk						
XALKORI	173	93	38	11	2	0
Chemotherapy	174	49	15	4	1	0

Patient reported symptoms and global QOL was collected using the EORTC QLQ-C30 and its lung cancer module (EORTC QLQ-LC13) at baseline (Day 1 Cycle 1) and Day 1 of each subsequent treatment cycle. A total of 162 patients in the crizotinib arm and 151 patients in the chemotherapy arm had completed the EORTC QLQ-C30 and LC13 questionnaires at baseline and at least 1 post baseline visit.

TTD was pre-specified as the time from randomization to the first occurrence of a ≥10-point increase in scores from baseline in symptoms of pain (EORTC QLQ-LC13 pain in chest), cough (EORTC QLQ-LC13 cough), or dyspnea (EORTC QLQ-LC13 dyspnea). The median TTD in patient-reported pain in chest, dyspnea, or cough as a composite endpoint was 4.5 months (95% CI: 3.0 months, 6.9 months) in the crizotinib arm compared to 1.4 months (95% CI: 1.0 months, 1.6 months) in the chemotherapy arm. Treatment with crizotinib was associated with a significantly longer TTD in the symptoms of pain in chest, dyspnea, or cough compared to chemotherapy (hazard ratio 0.50; 95% CI: 0.37, 0.66; Hochberg-adjusted log-rank p-value <0.0001).

The change from baseline scores was found to be significantly different between the 2 treatment arms, with a significantly greater improvement observed in global quality of life in the crizotinib arm compared to the chemotherapy arm (overall difference in change from baseline scores 9.84; p-value <0.0001).

Figure 5. Kaplan-Meier Plot of Time to Deterioration in Pain (in Chest), Dyspnea, or Cough (Composite Endpoint) by Treatment Arm (Patient-Reported Outcome Evaluable Population) in Patients With Previously Treated ALK-Positive Advanced NSCLC



Number at Risk						
XALKORI	161	54	20	8	1	0
Chemotherapy	150	15	5	1	0	

Single-Arm Studies in ALK-Positive Advanced NSCLC

The use of single-agent XALKORI in the treatment of ALK-positive advanced NSCLC with or without brain metastases was investigated in 2 multicenter, multinational, single-arm studies (Studies 1001 and 1005). Patients enrolled into these studies had received prior systemic therapy, with the exception of 16 patients in Study 1001 and 3 patients in Study 1005 who had no prior systemic treatment for locally advanced or metastatic disease. The primary efficacy endpoint in both studies was ORR according to RECIST. Secondary endpoints included Time to Tumor Response (TTR), DR, PFS, and OS. Patients received XALKORI 250 mg orally twice daily.

In Study 1001 (N=119), the demographic characteristics were 50% female; median age 51 years; baseline ECOG performance status of 0 or 1 (87%) or 2 (12%), 62% White and 29% Asian; <1% current smokers, 27% former-smokers, and 72% never smokers. The disease characteristics were 96% metastatic, 98% adenocarcinoma histology, and 13% with no prior systemic therapy for metastatic disease.

In Study 1005 (N=934), the demographic characteristics were 57% female; median age 53 years; baseline ECOG performance status of 0/1 (82%) or 2/3 (18%), 52% White and 44% Asian; and, 4% current smokers, 30% former smokers, and 66% never smokers. The disease characteristics were 92% metastatic, 94% adenocarcinoma histology.

In Study 1001, 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 patients with ALK-positive advanced NSCLC were enrolled into Study 1001 at the time of data cutoff for the PFS and ORR analyses. The median duration of treatment was 32 weeks. There were 2 complete responses and 69 partial responses for an ORR of 61%. The median DR was 48 weeks. Fifty-five percent of objective tumor responses were achieved during the first 8 weeks of treatment. Study 1001 OS data were updated based on 154 ALK-positive advanced NSCLC patients. The median OS at the time of data cutoff was 28.9 months (95% CI: 21.1, 40.1).

In Study 1005, patients with advanced NSCLC were required to have ALK-positive tumors prior to entering the clinical trial. For most patients, ALK-positive NSCLC was identified by FISH.

Nine hundred thirty-four patients with ALK-positive advanced NSCLC were treated with crizotinib in Study 1005 at the time of data cutoff for the PFS and ORR analyses. 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 crizotinib treatment for at least 3 weeks after objective disease progression.

Seven hundred sixty-five patients with ALK-positive advanced NSCLC from Study 1005 were both evaluable for response and identified by the same FISH assay used in randomized Phase 3 Study 1007. There were 8 complete responses and 357 partial responses for an ORR of 48%. The median DR was 47 weeks. Eighty-three percent of objective tumor responses were achieved within the first 12 weeks of treatment. Study 1005 OS data were updated based on 905 ALK-positive advanced NSCLC patients identified by the same FISH assay used in randomized Phase 3 Study 1007. The median OS at the time of data cutoff was 21.5 months (95% CI: 19.3, 23.6).

Efficacy data from Studies 1001 and 1005 are provided in Table 6.

Table 6. ALK-Positive Advanced NSCLC Efficacy Results From Studies 1001 and 1005

Efficacy Parameter	Study 1001	Study 1005
	N=119[a]	**N=765[a]**
ORR[b] [% (95% CI)]	61 (52, 70)	48 (44, 51)
TTR [median (range)] weeks	7.7 (4, 40)	6.1 (3, 49)
DR[c] [median (95% CI)] weeks	48.1 (36, not reached)	47.3 (36, 54)
PFS[c] [median (95% CI)] months	10.0 (8.2, 14.7)	7.8 (6.9, 9.5)[d]
	N=154[e]	**N=905[e]**
Number of deaths, n (%)	83 (54%)	504 (56%)
OS[c] [median (95% CI)] months	28.9 (21.1, 40.1)	21.5 (19.3, 23.6)

Abbreviations: N/n=number of patients; CI=confidence interval; ORR=objective response rate; TTR=time to tumor response; DR=duration of response; PFS=progression-free survival; OS=overall survival.

a. Per data cutoff dates 15 September 2010 (Study 1001) and 15 February 2012 (Study 1005).
b. Three patients were not evaluable for response in Study 1001, and 42 patients were not evaluable for response in Study 1005.
c. Estimated using the Kaplan-Meier method.
d. PFS data from Study 1005 included 807 patients in the safety analysis population who were identified by the FISH assay (per data cutoff date 15 February 2012).
e. Per data cutoff date 30 November 2013.

ROS1-Positive Advanced NSCLC

The use of single-agent crizotinib in the treatment of ROS1-positive advanced NSCLC was investigated in multicenter, multinational, single-arm Study 1001. A total of 53 ROS1-positive advanced NSCLC patients were enrolled in the study at the time of data cutoff, including 46 patients with previously treated ROS1-positive advanced NSCLC and 7 patients who had no prior systemic treatment. The primary efficacy endpoint was ORR according to RECIST. Secondary endpoints included TTR, DR, PFS, and OS. Patients received crizotinib 250 mg orally twice daily.

The demographic characteristics were 57% female; median age 55 years; baseline ECOG performance status of 0 or 1 (98%) or 2 (2%), 57% White and 40% Asian; 25% former smokers, and 75% never smokers. The disease characteristics were 94% metastatic, 96% adenocarcinoma histology, and 13% with no prior systemic therapy for metastatic disease.

In Study 1001, patients were required to have ROS1-positive advanced NSCLC prior to entering the clinical trial. For most patients, ROS1-positive NSCLC was identified by FISH. The median duration of treatment was 22.4 months (95% CI: 15.0, 35.9). There were 6 complete responses and 32 partial responses for an ORR of 72% (95% CI: 58%, 83%). The median DR was 24.7 months (95% CI: 15.2, 45.3). Fifty percent of objective tumor responses were achieved during the first 8 weeks of treatment. The median PFS at the time of data cutoff was 19.3 months (95% CI: 15.2, 39.1). The median OS at the time of data cutoff was 51.4 months (95% CI: 29.3, NR).

Efficacy data from ROS1-positive advanced NSCLC patients from Study 1001 are provided

in Table 7.

Table 7. ROS1-Positive Advanced NSCLC Efficacy Results From Study 1001

Efficacy Parameter	Study 1001
	N=53[a]
ORR [% (95% CI)]	72 (58, 83)
TTR [median (range)] weeks	8 (4, 104)
DR[b] [median (95% CI)] months	24.7 (15.2, 45.3)
PFS[b] [median (95% CI)] months	19.3 (15.2, 39.1)
OS[b] [median (95% CI)] months	51.4 (29.3, NR)

Abbreviations: N=number of patients; CI=confidence interval; ORR=objective response rate; NR=not reached; TTR=time to tumor response; DR=duration of response; OS=overall survival; PFS=progression-free survival.
OS is based on a median follow up of approximately 63 months.
a. Per data cutoff date30 June 2018.
b. Estimated using the Kaplan-Meier method.

Elderly (see also Sections **Posology and Method of Administration** and **Pharmacokinetic Properties**)
Of 171 ALK-positive NSCLC patients treated with crizotinib in randomized Phase 3 Study 1014, 22 (13%) were 65 years or older, and of the 109 patients treated with crizotinib who crossed over from the chemotherapy arm, 26 (24%) were 65 years or older. Of the 172 patients treated with crizotinib in randomized Phase 3 Study 1007, 27 (16%) were 65 years or older. Of 154 and 1063 ALK-positive NSCLC patients in single arm studies 1001 and 1005, 22 (14%) and 173 (16%) were 65 years or older, respectively. In ALK-positive NSCLC patients, the frequency of adverse reactions was generally similar for patients <65 years of age and patients ≥65 years of age with the exception of edema and constipation, which were reported with greater frequency in a randomized study among patients treated with crizotinib ≥65 years of age. No overall differences in efficacy were observed in comparison with younger patients. Of the 53 ROS1-positive NSCLC patients in single arm Study 1001, 15 (28%) were 65 years of older.

Pharmacokinetic Properties
Absorption
Following oral single dose administration in the fasted state, crizotinib is absorbed with median time to achieve peak concentrations of 4 to 6 hours. Following crizotinib 250 mg twice daily, steady-state was reached within 15 days and remained stable, with a median accumulation ratio of 4.8. The absolute bioavailability of crizotinib was determined to be 43% (range: 32% to 66%) following the administration of a single 250 mg oral dose.

A high-fat meal reduced crizotinib area under the plasma concentration-time curve from time zero to infinity (AUC_{inf}) and maximum observed plasma concentration (C_{max}) by approximately 14% when a 250 mg single dose was given to healthy volunteers. Crizotinib

can be administered with or without food (see Section **Posology and Method of Administration**).

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.

Binding of crizotinib to human plasma proteins *in vitro* is 91% and is independent of drug concentration. *In vitro* studies suggested that crizotinib is a substrate for P-glycoprotein (P-gp). The blood-to-plasma concentration ratio is approximately 1.

Metabolism
In vitro studies demonstrated that 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.

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

Elimination
Following single doses of crizotinib, the apparent plasma terminal half-life of crizotinib was 42 hours in patients.

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

The mean apparent clearance (CL/F) of crizotinib was lower at steady-state (60 L/hr) after 250 mg twice daily than that after a single 250 mg oral dose (100 L/hr), which was likely due to autoinhibition of CYP3A by crizotinib after multiple dosing.

Drug Interactions
Co-administration of Crizotinib and CYP3A Substrates
Crizotinib has been identified as an inhibitor of CYP3A both *in vitro* and *in vivo*. Following 28 days of crizotinib dosing at 250 mg taken twice daily in cancer patients, the oral midazolam AUC_{inf} was 3.7-fold (90% CI: 2.63-5.07) those seen when midazolam was administered alone, suggesting that crizotinib is a moderate inhibitor of CYP3A (see Section **Interaction with Other Medicinal Products and Other Forms of Interaction**).

Co-administration of Crizotinib and CYP3A Inhibitors

Coadministration of crizotinib (250 mg once daily) with itraconazole (200 mg once daily), a strong CYP3A inhibitor, resulted in 57% and 33% increases in crizotinib steady-state area under the plasma concentration-time curve from 0 hour to time tau, the dosing interval (AUC_{tau}) and C_{max}, respectively, compared to when crizotinib was given alone. Co-administration of a single 150 mg oral dose of crizotinib in the presence of ketoconazole (200 mg twice daily), a strong CYP3A inhibitor, resulted in increases in crizotinib systemic exposure, with crizotinib AUC_{inf} and C_{max} values that were approximately 3.2-fold and 1.4-fold, respectively, those seen when crizotinib was administered alone. However, the magnitude of effect of CYP3A inhibitors on steady-state crizotinib exposure has not been established (see Section **Interaction with Other Medicinal Products and Other Forms of Interaction**).

Co-administration of Crizotinib and CYP3A Inducers
Co-administration of crizotinib (250 mg twice daily) with rifampin (600 mg once daily), a strong CYP3A inducer, resulted in 84% and 79% decreases in crizotinib steady-state AUC_{tau} and C_{max}, respectively, compared to when crizotinib was given alone (see Section **Interaction with Other Medicinal Products and Other Forms of Interaction**).

Co-administration of Crizotinib with Agents that Increase Gastric pH
The aqueous solubility of crizotinib is pH dependent, with low (acidic) pH resulting in higher solubility. Administration of a single 250 mg crizotinib dose following treatment with esomeprazole 40 mg once daily for 5 days resulted in an approximately 10% decrease in crizotinib total exposure (AUC_{inf}) and no change in peak exposure (C_{max}); the extent of the change in total exposure was not clinically meaningful. Therefore, starting dose adjustment is not required when crizotinib is coadministered with agents that increase gastric pH (such as proton-pump inhibitors, H_2 blockers, or antacids).

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

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. *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.

Co-administration with UGT 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 uridine diphosphate glucuronosyltransferase (UGT)1A1, UGT1A4, UGT1A6, UGT1A9 or UGT2B7.

Co-administration with Drugs that are Substrates of Transporters
Crizotinib is an inhibitor of P-glycoprotein (P-gp) *in vitro*. Therefore, crizotinib may have the potential to increase plasma concentrations of co-administered drugs that are substrates of P-gp.

Crizotinib is an inhibitor of OCT1 and OCT2 *in vitro*. Therefore, crizotinib may have the potential to increase plasma concentrations of co-administered drugs that are substrates of OCT1 or OCT2.

In vitro, crizotinib did not inhibit the human hepatic uptake transport proteins organic anion transporting polypeptide (OATP)1B1 or OATP1B3, or the renal uptake transport proteins organic anion transporter (OAT)1 or OAT3 at clinically relevant concentrations. Therefore, clinical drug-drug interactions are unlikely to occur as a result of crizotinib-mediated inhibition of the hepatic or renal uptake of drugs that are substrates for these transporters.

Effect on Other Transport Proteins
In vitro, crizotinib is not an inhibitor of BSEP at clinically relevant concentrations.

Pharmacokinetics in special patient groups
Hepatic Impairment: Crizotinib is extensively metabolized in the liver. Patients with mild (either AST >ULN and total bilirubin ≤ULN or any AST and total bilirubin >ULN but ≤1.5×ULN), moderate (any AST and total bilirubin >1.5×ULN and ≤3×ULN), or severe (any AST and total bilirubin >3×ULN) hepatic impairment or normal (AST and total bilirubin ≤ULN) hepatic function, who were matched controls for mild or moderate hepatic impairment, were enrolled in an open-label, non-randomized clinical study (Study 1012), based on NCI classification.

Following crizotinib 200 mg twice daily dosing, patients with moderate hepatic impairment (N=8) showed higher systemic crizotinib exposure compared to patients with normal hepatic function (N=9) at the same dose level, with geometric mean ratios for AUC_{daily} and C_{max} of 150% and 144%, respectively. However, the systemic crizotinib exposure in patients with moderate hepatic impairment at the dose of 200 mg twice daily was comparable to that observed from patients with normal hepatic function at a dose of 250 mg twice daily, with geometric mean ratios for AUC_{daily} and C_{max} of 114% and 109%, respectively.

The systemic crizotinib exposure parameters AUC_{daily} and C_{max} in patients with severe hepatic impairment (N=6) receiving a crizotinib dose of 250 mg once daily were approximately 64.7% and 72.6%, respectively, of those from patients with normal hepatic function receiving a dose of 250 mg twice daily.

An adjustment of the dose of crizotinib is recommended when administering crizotinib to patients with moderate or severe hepatic impairment (see Sections **Posology and Method of Administration** and **Special Warnings and Precautions for Use**).

Renal Impairment: Patients with mild ($60 \leq CL_{cr} < 90$ mL/min) and moderate ($30 \leq CL_{cr} < 60$ mL/min) renal impairment were enrolled in single-arm Studies 1001 and 1005. The effect of renal function as measured by baseline CL_{cr} on observed crizotinib steady-state trough concentrations ($C_{trough, ss}$) was evaluated. In Study 1001, the adjusted geometric mean of plasma $C_{trough, ss}$ in mild (N = 35) and moderate (N = 8) renal impairment patients were 5.1% and 11% higher, respectively, than those in patients with normal renal function. In Study 1005, the adjusted geometric mean $C_{trough, ss,}$ of crizotinib in mild (N = 191) and moderate (N = 65) renal impairment groups were 9.1% and 15% higher, respectively, than those in patients with normal renal function. In addition, the population pharmacokinetic analysis from Studies 1001, 1005 and 1007 indicated CL_{cr} did not have a clinically meaningful effect on the pharmacokinetics of crizotinib. Due to the small size of the increases in crizotinib exposure (5%-15%), no starting dose adjustment is recommended for patients with mild or moderate renal impairment. After a single 250-mg dose in subjects with severe renal impairment (CL_{cr} <30 mL/min) not requiring peritoneal dialysis or hemodialysis, crizotinib AUC_{inf} and C_{max} increased by 79% and 34%, respectively, compared to those with normal renal function. An adjustment of the dose of crizotinib is recommended when administering crizotinib to patients with severe renal impairment not requiring peritoneal dialysis or hemodialysis (see Sections **Posology and Method of Administration** and **Special Warnings and Precautions for Use**).

Age: Based on the population pharmacokinetic analysis from Studies 1001, 1005 and 1007, age has no effect on crizotinib pharmacokinetics (see Sections **Posology and Method of Administration** and **Pharmacodynamic Properties**).

Body Weight and Gender: Based on the population pharmacokinetic analysis from Studies 1001, 1005 and 1007, there was no clinically meaningful effect of body weight or gender on crizotinib pharmacokinetics.

Ethnicity: Based on the population pharmacokinetic analysis from Studies 1001, 1005 and 1007, the predicted area under the plasma concentration-time curve at steady-state (AUC_{ss}) (95% CI) was 23%-37% higher in Asian patients (n = 523) than in non-Asian patients (n = 691).

Cardiac electrophysiology
The QT interval prolongation potential of crizotinib was assessed in patients with either ALK-positive or ROS1-positive NSCLC who received crizotinib 250 mg twice daily. Serial ECGs in triplicate were collected following a single dose and at steady-state to evaluate the effect of crizotinib on QT intervals. Thirty-four of 1619 patients (2.1%) with at least 1 postbaseline ECG assessment were found to have QTcF (corrected QT by the Fridericia method) ≥500 msec, and 79 of 1585 patients (5.0%) with a baseline and at least 1 postbaseline ECG assessment had an increase from baseline QTcF ≥60 msec by automated machine-read evaluation of ECG (see Section **Special Warnings and Precautions for Use**).

An ECG substudy using blinded manual ECG measurements was conducted in 52 ALK-positive NSCLC patients who received crizotinib 250 mg twice daily. A central tendency analysis indicated that a QTc effect ≥20 msec can be excluded. A pharmacokinetic/pharmacodynamic analysis suggested a relationship between crizotinib plasma concentration and QTc. In addition, a decrease in heart rate was found to be associated with increasing crizotinib plasma concentration (see Section **Special Warnings and Precautions for Use**).

Preclinical Safety Data
In rat and dog repeat-dose toxicity studies up to 3 months duration, the primary target organ effects were related to the gastrointestinal (emesis, fecal changes, congestion), hematopoietic (bone marrow hypocellularity), cardiovascular (mixed ion channel blocker, decreased heart rate and blood pressure, increased LVEDP, QRS and PR intervals, and decreased myocardial contractility), or reproductive (testicular pachytene spermatocyte degeneration, single-cell necrosis of ovarian follicles) systems. The No Observed Adverse Effect Levels (NOAEL) for these findings were either subtherapeutic or up to 5-fold human clinical exposure based on AUC. Other findings included an effect on the liver (elevation of liver transaminases) and retinal function, and potential for phospholipidosis in multiple organs without correlative toxicities.

Crizotinib was not mutagenic *in vitro* in the bacterial reverse mutation (Ames) assay. Crizotinib was aneugenic in an *in vitro* micronucleus assay in Chinese Hamster Ovary cells and in an *in vitro* human lymphocyte chromosome aberration assay. Small increases of structural chromosomal aberrations at cytotoxic concentrations were seen in human lymphocytes. The NOAEL for aneugenicity was approximately 4-fold human clinical exposure based on AUC.

Carcinogenicity studies with crizotinib have not been performed.

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 ≥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. Post-implantation loss was increased at doses ≥50 mg/kg/day (approximately 0.8 times the AUC at the recommended human dose) in rats, and 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).

Decreased bone formation in growing long bones was observed in immature rats at 150 mg/kg/day following once daily dosing for 28 days (approximately 7 times human clinical exposure based on AUC). Other toxicities of potential concern to paediatric patients have not been evaluated in juvenile animals.

The results of an *in vitro* phototoxicity study demonstrated that crizotinib may have phototoxic potential.

PHARMACEUTICAL PARTICULARS

List of Excipients

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.

Incompatibilities

Not applicable.

Supply

XALKORI® 200 mg;
Box of 1 blister @10 capsules; Reg. No.: DKI1390701501A2

XALKORI® 250 mg;
Box of 1 blister @10 capsules; Reg. No.: DKI1390701501B2

Store below 30°C.

HARUS DENGAN RESEP DOKTER

Manufactured by:
Pfizer Manufacturing Deutschland GmbH
Freiburg, Germany

Imported by:
PT. Pfizer Indonesia
Jakarta, Indonesia

Leaflet kemasan: informasi bagi pengguna

XALKORI® 200 mg kapsul
XALKORI® 250 mg kapsul
Crizotinib

Bacalah seluruh isi leaflet ini dengan saksama sebelum Anda mulai meminum obat ini karena leaflet ini memuat informasi penting untuk Anda.
- Simpan leaflet ini. Anda mungkin perlu membacanya kembali.
- Jika Anda memiliki pertanyaan lebih lanjut, hubungi dokter, apoteker, atau perawat Anda.
- Obat ini telah diresepkan hanya untuk Anda. Jangan memberikannya kepada orang lain. Obat ini dapat membahayakan mereka, sekalipun gejala-gejala penyakit mereka sama dengan Anda.
- Jika Anda mengalami efek samping, konsultasikan dengan dokter, apoteker, atau perawat Anda. Termasuk segala bentuk kemungkinan efek samping yang tidak dicantumkan di dalam leaflet ini.

Isi leaflet ini

1. Penjelasan tentang XALKORI dan kegunaannya

XALKORI adalah obat antikanker yang mengandung zat aktif crizotinib yang digunakan untuk mengobati pasien dewasa penderita kanker paru yang disebut kanker paru non-sel kecil, yang muncul dengan penyusunan ulang atau kerusakan spesifik dalam gen yang disebut limfoma kinase anaplastik (ALK), atau dalam gen yang disebut ROS1.

XALKORI dapat diresepkan sebagai pengobatan Anda jika penyakit Anda sudah berada pada kanker paru stadium lanjut.

XALKORI dapat diresepkan kepada Anda jika penyakit Anda sudah berada pada stadium lanjut dan terapi sebelumnya tidak dapat menghentikan perkembangan penyakit Anda.

XALKORI dapat memperlambat atau menghentikan pertumbuhan kanker paru. Obat ini dapat membantu menyusutkan sel-sel tumor.

XALKORI harus diresepkan oleh profesional kesehatan terkualifikasi yang telah berpengalaman dalam penggunaan terapi anti-neoplastik.

Jika Anda memiliki pertanyaan terkait cara kerja XALKORI atau alasan mengapa obat ini diresepkan untuk Anda, silakan tanyakan kepada dokter Anda.

2. Hal yang perlu Anda ketahui sebelum meminum XALKORI

Jangan meminum XALKORI

- Jika Anda alergi terhadap crizotinib atau bahan lain yang ada di dalam obat ini (tercantum dalam Bagian 6 "Kandungan XALKORI"), maka jangan meminum obat ini.
- Jika Anda mengidap penyakit hati yang parah.

Peringatan dan tindakan pencegahan
Konsultasikan dengan dokter Anda sebelum meminum XALKORI:

- Jika Anda pernah menderita penyakit hati ringan atau sedang.
- Jika Anda pernah mengalami gangguan paru lainnya. Beberapa gangguan paru dapat bertambah parah selama pengobatan dengan XALKORI, sebab XALKORI dapat menyebabkan inflamasi paru selama pengobatan. Gejala-gejalanya mungkin serupa dengan gejala kanker paru. Segera beritahukan dokter jika Anda mengalami gejala baru atau gejala yang bertambah parah di antaranya kesulitan bernapas atau napas tersengal, batuk dengan atau tanpa mukus atau demam.
- Jika Anda pernah diberi tahu perihal adanya abnormalitas pada rekam jantung Anda setelah menjalani elektrokardiogram (EKG) yang disebut dengan interval QT berkepanjangan.
- Jika Anda mengidap penurunan denyut jantung.
- Jika Anda pernah mengalami gangguan pada lambung atau usus seperti berlubang (perforasi), atau jika Anda mengidap kondisi yang menyebabkan inflamasi di dalam abdomen (divertikulitis), atau jika Anda mempunyai penyebaran kanker di dalam abdomen (metastasis).
- Jika Anda memiliki gangguan penglihatan (melihat kilatan cahaya, penglihatan kabur, dan penglihatan ganda).
- Jika Anda mengidap penyakit ginjal yang parah.
- Jika saat ini Anda meminum salah satu obat yang tercantum dalam bagian **Obat-obatan lain dan XALKORI.**

Segera konsultasikan dengan dokter Anda setelah meminum XALKORI:

- Jika Anda mengalami nyeri perut atau abdomen yang parah, demam, menggigil, napas tersengal, denyut jantung cepat, kehilangan penglihatan sebagian atau seluruhnya (pada salah satu atau kedua mata), atau perubahan dalam kebiasaan buang air besar.

Sebagian besar informasi yang tersedia adalah untuk pasien dengan beberapa jenis histologi spesifik dari NSCLC ALK-positif (adenokarsinoma) dan informasi terbatas tersedia dalam histologi lainnya.

Anak-anak dan remaja
Tidak disarankan mengobati anak-anak dan remaja dengan obat ini. Indikasi ini tidak mencakup anak-anak dan remaja.

Obat-obatan lain dan XALKORI
Beritahukan dokter atau apoteker jika Anda juga meminum, dan baru saja meminum atau mungkin meminum obat-obatan lain, termasuk obat-obatan herbal dan obat-obatan yang diperoleh secara bebas.

Secara khusus, obat-obatan berikut dapat meningkatkan risiko efek samping XALKORI:

- Klaritromisin, telitromisin, troleandomisin, antibiotik yang digunakan untuk mengobati infeksi bakteri.

- Ketokonazol, itrakonazol, vorikonazol, yang digunakan untuk mengobati infeksi jamur.
- Atazanavir, indinavir, nelfinavir, ritonavir, saquinavir, yang digunakan untuk mengobati infeksi HIV/AIDS.

Obat-obatan berikut dapat mengurangi efektivitas XALKORI:
- Fenitoin, karbamazepin, atau fenobarbital, anti-epilepsi yang digunakan untuk mengobati kejang.
- Rifabutin, rifampisin, yang digunakan untuk mengobati tuberkulosis.
- St. John's Wort (*Hypericum perforatum*), sebuah produk herbal yang digunakan untuk mengobati depresi.

XALKORI dapat meningkatkan efek samping yang berhubungan dengan obat-obatan berikut:
- Alfentanil, dan opiat kerja singkat lainnya seperti fentanil (pereda nyeri yang digunakan untuk prosedur bedah).
- Kuinidin, digoksin, disopiramid, amiodaron, sotalol, dofetilid, ibutilid, verapamil, diltiazem yang digunakan untuk mengobati gangguan jantung.
- Pimozid, yang digunakan untuk mengobati penyakit mental.
- Cisaprid, yang digunakan untuk mengobati gangguan perut.
- Siklosporin, sirolimus, dan takrolimus yang digunakan pada pasien transplantasi.
- Alkaloid ergot (misalnya ergotamin, dihidroergotamin), yang digunakan untuk mengobati migrain.
- Dabigatran, antikoagulan yang digunakan untuk memperlambat pembekuan darah.
- Kolkisin, yang digunakan untuk mengobati pirai.
- Pravastatin, yang digunakan untuk menurunkan kadar kolesterol.
- Obat darah tinggi yang disebut beta-blocker seperti atenolol, propranolol, labetolol.
- Metformin, digunakan untuk mengobati diabetes.
- Procainamide, digunakan untuk mengobati aritmia jantung.
- Clonidine, guanfacine, digunakan untuk mengobati hipertensi.
- Mefloquine, digunakan untuk pencegahan malaria.
- Pilocarpine, digunakan untuk mengobati glaukoma (penyakit mata yang parah).
- Antikolinesterase, digunakan untuk mengembalikan fungsi otot.
- Antipsikotik, digunakan untuk mengobati penyakit mental.
- Moxifloxacine, digunakan untuk mengobati infeksi bakteri.
- Metadon, digunakan untuk mengobati rasa sakit dan untuk pengobatan ketergantungan opioid.
- Bupropion, digunakan untuk mengobati depresi dan berhenti merokok.
- Efavirenz, raltegravir, digunakan untuk mengobati infeksi HIV.
- Irinotecan, obat kemoterapi yang digunakan untuk mengobati kanker usus besar dan rektum.
- Morfin, digunakan untuk mengobati nyeri akut dan kanker.
- Nalokson, digunakan untuk mengobati kecanduan dan penarikan obat opiat.

Oleh karena itu, obat-obatan ini *harus dihindari* selama Anda menjalani pengobatan dengan XALKORI.

Pil kontrasepsi
Jika Anda meminum XALKORI selama menggunakan pil kontrasepsi, maka pil kontrasepsi tersebut mungkin tidak akan berfungsi efektif.

Antasida
Jika Anda meminum XALKORI bersama obat-obat yang dapat menetralkan asam lambung (seperti golongan penghambat pompa proton, pemblokir H_2 , atau antasida), maka kemungkinan akan menurunkan kelarutan XALKORI dan mengurangi ketersediaannya dalam tubuh Anda.

XALKORI dengan makanan dan minuman
Anda dapat meminum XALKORI sebelum atau sesudah makan; akan tetapi, Anda harus menghindari mengonsumsi jus grapefruit atau memakan grapefruit saat menjalani pengobatan dengan XALKORI sebab dapat mengubah kadar XALKORI dalam tubuh Anda.

Perlindungan matahari
Hindari menghabiskan waktu lama di bawah sinar matahari. XALKORI dapat membuat kulit Anda sensitif terhadap sinar matahari (fotosensitifitas), dan Anda mungkin lebih mudah terbakar. Anda harus mengenakan pakaian pelindung dan/atau menggunakan tabir surya yang menutupi kulit Anda untuk membantu melindungi dari sengatan matahari jika Anda harus berada di bawah sinar matahari selama perawatan dengan XALKORI.

Kehamilan dan menyusui
Konsultasikan dengan dokter atau apoteker Anda sebelum meminum obat ini jika Anda hamil, atau berpeluang untuk hamil atau sedang menyusui.

Disarankan agar wanita tidak hamil dan pria tidak melakukan pembuahan saat menjalani pengobatan dengan XALKORI, sebab XALKORI dapat membahayakan janin. Jika orang yang meminum obat ini berpeluang untuk hamil atau membuahi sel telur, maka mereka harus menggunakan kontrasepsi yang memadai selama menjalani pengobatan, dan sedikitnya selama 90 hari setelah menyelesaikan terapi sebab pil kontrasepsi mungkin tidak akan bekerja efektif selama pasien meminum XALKORI.

Jangan menyusui selama Anda menjalani pengobatan dengan XALKORI. XALKORI dapat membahayakan bayi yang diberi ASI tersebut.

Jika Anda hamil atau menyusui, mengira bahwa diri Anda sedang hamil atau berencana untuk hamil, mintalah saran dari dokter atau apoteker Anda sebelum meminum obat ini.

Mengemudi dan mengoperasikan mesin
Anda harus sangat berhati-hati saat mengemudi dan mengoperasikan mesin, sebab pasien yang meminum XALKORI dapat mengalami gangguan penglihatan, pusing, dan kelelahan.

3. Cara meminum XALKORI

Selalu minum obat ini dengan tepat sesuai petunjuk dokter Anda. Tanyakan kepada dokter atau apoteker jika Anda merasa tidak yakin.

- Dosis yang disarankan adalah satu kapsul 250 mg diminum secara oral dua kali sehari (total 500 mg).
- Minum kapsul satu kali di pagi hari dan satu kali di malam hari.
- Minum kapsul pada waktu yang kurang lebih sama setiap hari.
- Anda dapat meminum kapsul sebelum atau sesudah makan dan selalu hindari mengonsumsi buah grapefruit.
- Telan kapsul secara utuh dan jangan menggerusnya, melarutkannya atau membuka

kapsulnya.

Bila perlu, dokter dapat memutuskan untuk menurunkan dosis Anda ke 200 mg secara oral dua kali sehari (total 400 mg) dan apabila penurunan dosis lebih lanjut perlu dilakukan, maka dokter akan menurunkannya menjadi 250 mg secara oral satu kali sehari. Dokter Anda dapat memutuskan untuk menghentikan pengobatan Anda secara permanen jika Anda tidak dapat menoleransi XALKORI 250 mg secara oral satu kali sehari.

Jika Anda meminum XALKORI melebihi dosis yang disarankan
Jika Anda tidak sengaja meminum kapsul melebihi yang disarankan, informasikan kepada dokter atau apoteker Anda secepatnya. Anda mungkin memerlukan penanganan medis.

Jika Anda lupa meminum XALKORI
Yang harus dilakukan jika Anda lupa meminum kapsul bergantung pada berapa lama selang waktu hingga dosis berikutnya.

- Jika jarak dosis Anda berikutnya adalah dalam waktu **6 jam atau lebih,** minumlah kapsul yang terlewat sesegera mungkin setelah Anda teringat. Lalu minum kapsul berikutnya pada jadwal semestinya.
- Jika jarak dosis Anda berikutnya adalah **kurang dari 6 jam,** maka lewati saja kapsul yang terlupa. Lalu minum kapsul berikutnya pada jadwal semestinya.

Beritahukan dokter Anda mengenai dosis yang terlewat tersebut pada kunjungan berikutnya.

Jangan meminum dosis ganda (dua kapsul secara bersamaan) sebagai pengganti kapsul yang terlupa.

Jika Anda berhenti meminum XALKORI
Penting untuk meminum XALKORI setiap hari, sepanjang dokter meresepkannya untuk Anda. Jika Anda tidak dapat meminum obat tersebut sebagaimana yang diresepkan oleh dokter, atau Anda merasa tidak memerlukannya lagi, segera hubungi dokter Anda.

Jika Anda memiliki pertanyaan lebih lanjut seputar penggunaan obat ini, tanyakan kepada dokter atau apoteker Anda.

4. Kemungkinan efek samping

Seperti semua obat-obatan yang ada, obat ini dapat menimbulkan efek samping, meskipun tidak semua orang mengalaminya.

Jika Anda mengalami efek samping, konsultasikan dengan dokter, apoteker, atau perawat Anda. Termasuk segala bentuk efek samping yang tidak dicantumkan di dalam leaflet ini.

Beberapa efek samping dapat bersifat serius. Anda harus segera menghubungi dokter Anda jika mengalami salah satu efek samping serius berikut ini (lihat juga bagian 2 "Hal yang perlu Anda ketahui sebelum meminum XALKORI"):

- **Fungsi hati abnormal**
  Segera beri tahu dokter jika Anda merasa lebih lelah daripada biasanya, kulit dan bagian putih pada mata berubah menjadi kuning, air seni menjadi gelap atau coklat (warna teh), mengalami mual, muntah, atau mengalami penurunan nafsu makan, mengalami nyeri di bagian kanan perut, mengalami gatal, atau jika luka lebam lebih mudah muncul dibandingkan biasanya. Dokter dapat melakukan tes darah untuk memeriksa fungsi hati Anda, dan jika hasilnya abnormal, dokter dapat memutuskan

untuk menurunkan dosis XALKORI atau menghentikan pengobatan Anda.

- **Inflamasi paru**
  Segera beritahu dokter jika Anda mengalami kesulitan bernapas, khususnya jika disertai dengan batuk atau demam.

- **Penurunan jumlah sel darah putih (termasuk neutrofil)**
  Segera beri tahu dokter jika Anda mengalami demam atau infeksi. Dokter dapat melakukan tes darah dan jika hasilnya abnormal, dokter dapat memutuskan untuk menurunkan dosis XALKORI.

- **Sakit kepala ringan, pingsan, atau rasa tidak nyaman di dada**
  Segera beri tahu dokter jika Anda mengalami gejala-gejala ini yang bisa jadi merupakan tanda-tanda perubahan aktivitas listrik (terlihat pada elektrokardiogram) atau irama jantung yang abnormal. Dokter dapat melakukan elektrokardiogram untuk memastikan tidak adanya masalah pada jantung Anda selama pengobatan dengan XALKORI.

- **Kehilangan penglihatan sebagian atau seluruhnya pada salah satu atau kedua mata**
  Segera beri tahu dokter jika Anda mengalami kehilangan penglihatan atau perubahan dalam penglihatan seperti kesulitan untuk melihat dengan salah satu atau kedua mata. Dokter Anda dapat menghentikan pengobatan dengan XALKORI dan merujuk Anda kepada dokter spesialis mata.

Efek samping lain dari XALKORI dapat meliputi:

Efek samping yang sangat umum (dapat dialami oleh lebih dari 1 orang di antara 10 pasien)
- Penurunan jumlah sel darah putih (yang penting untuk melawan infeksi).
- Abnormalitas dalam tes darah dan hati.
- Penurunan jumlah neutrofil.
  Gangguan penglihatan (melihat kilatan cahaya, penglihatan kabur, atau penglihatan ganda, sering kali dimulai tidak lama setelah memulai pengobatan dengan XALKORI).
- Neuropati (perasaan kebas atau seperti tertusuk pada persendian, ekstremitas, atau otot).
- Pusing.
- Kelelahan.
- Edema (cairan berlebih di dalam jaringan tubuh, sehingga menyebabkan pembengkakan tangan dan kaki).
- Gangguan perut, termasuk mual, muntah, diare, dan konstipasi.
- Penurunan nafsu makan.
- Perubahan ketajaman indra perasa/pengecap
- Ruam kulit.
- Penurunan denyut jantung

Efek samping yang umum (dapat dialami oleh 1 hingga 10 orang di antara 100 pasien)
- Gangguan pencernaan.
- Esofagitis.
- Peningkatan kadar alkalin fosfatase darah.

- Interval QT elektrokardiogram berkepanjangan .
- Penyakit paru interstisial.
- Pingsan.
- Kista ginjal.
- Peningkatan kreatinin darah.
- Penurunan testosteron darah.

Efek samping yang tidak umum (dapat dialami oleh 1 hingga 10 orang dari 1000 pasien)
- Gagal hati.
- Peningkatan kadar dalam darah untuk tes yang memeriksa kerusakan otot (kadar kreatin fosfokinase tinggi).

5. Cara menyimpan XALKORI

- Jauhkan obat ini dari pandangan dan jangkauan anak-anak
- Jangan menggunakan obat ini melewati tanggal kedaluwarsanya (EXP) yang tertera pada botol atau blister foil dan kotak kemasan. Tanggal kedaluwarsa mengacu pada hari terakhir di bulan yang bersangkutan
- Jangan gunakan obat dari kemasan yang rusak atau yang memperlihatkan tanda-tanda kerusakan

Jangan membuang obat melalui air limbah atau sampah rumah tangga. Tanyakan kepada apoteker cara membuang obat yang sudah tidak digunakan lagi. Langkah-langkah ini akan membantu melindungi lingkungan.

6. Isi kemasan dan informasi lainnya

Kandungan XALKORI

- Zat aktif dalam XALKORI adalah crizotinib. Kapsul XALKORI tersedia dalam berbagai kekuatan dosis.
  XALKORI 200 mg: setiap kapsul mengandung 200 mg crizotinib
  XALKORI 250 mg: setiap kapsul mengandung 250 mg crizotinib

- Bahan-bahan lainnya adalah:
  Isi kapsul: Koloidal silicon dioksida , mikrokristalin selulosa, kalsium fosfat dibasic anhidrat, sodium pati glikolat (Tipe A), magnesium stearat.
  Cangkang kapsul: gelatin, titanium dioksida (E171), dan besi oksida merah (E172).
  Tinta cetak: shellac, propilen glikol, larutan ammonia yang kuat, potasium hidroksida, dan besi oksida hitam (E172).

Tampilan XALKORI dan isi kemasannya

XALKORI 200 mg tersedia dalam bentuk kapsul gelatin keras dengan tutup merah muda dan badan putih, dengan teks tinta hitam “Pfizer” pada bagian tutup, “CRZ 200” pada badan kapsul.

XALKORI 250 mg tersedia dalam bentuk kapsul gelatin keras dengan tutup merah muda dan badan putih, dengan teks tinta hitam “Pfizer” pada bagian tutup, “CRZ 250” pada badan kapsul.

Obat ini tersedia dalam kemasan blister isi 10 kapsul; No. Reg: DKI1390701501A2(200 mg) & DKI1390701501B2(250 mg) dan kemasan blister isi 60 kapsul; No. Reg: DKI1390701501B2(250 mg).

Tidak semua ukuran kemasan tersedia di pasaran.

Simpan di bawah suhu 30°C.

HARUS DENGAN RESEP DOKTER

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