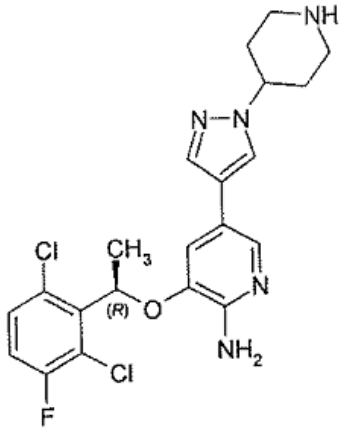
Crizotinib
Tradename: XALKORI

NAME OF THE MEDICINAL PRODUCT

XALKORI 250 mg; XALKORI 200 mg

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains either 250 mg or 200 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 previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (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 testing

Detection of ALK-positive NSCLC is necessary for selection of patients for treatment with crizotinib because these are the only patients for whom benefit has been shown.
Assessment for ALK-positive NSCLC should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. Improper assay performance can lead to unreliable test results.

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**). Capsules should be swallowed whole. 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, then the dose of crizotinib should be reduced to 200 mg taken orally twice daily, and if further dose reduction is necessary, then reduce the dosage to 250 mg taken orally once daily based on individual safety and tolerability. Dose reduction guidelines for hematologic and non-hematologic toxicities are provided in Tables 1 and 2.

Table 1. 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 200 mg twice daily[c]

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

[b]NCI Common Terminology Criteria for Adverse Events.

[c]In case of recurrence, withhold until recovery to Grade ≤2, then resume at 250 mg, once daily. Permanently discontinue in case of further Grade 4 recurrence.

Table 2. 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 200 mg twice daily[b]
Grade 2, 3 or 4 ALT or AST elevation with concurrent Grade 2, 3 or 4 total bilirubin elevation (in the absence of cholestasis or hemolysis)	Permanently discontinue
Any Grade pneumonitis[c]	Permanently discontinue
Grade 3 QTc prolongation	Withhold until recovery to Grade ≤ 1, then resume at 200 mg twice daily[b]
Grade 4 QTc prolongation	Permanently discontinue

[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]Not attributable to NSCLC progression, other pulmonary disease, infection, or radiation effect.

Hepatic impairment :
XALKORI has not been studied in patients with hepatic impairment. Clinical studies that were conducted excluded patients with AST or ALT >2.5 x upper limit of normal (ULN), or if due to underlying malignancy >5.0 x ULN or with total bilirubin >1.5 x ULN. Treatment with XALKORI should be used with caution in patients with mild and moderate hepatic impairment. XALKORI should not be used in patients with severe hepatic impairment.

Renal impairment :
No starting dose adjustment is recommended for patients with mild (creatinine clearance [CLcr] 60 to 90 mL/min) and moderate renal impairment (CLcr 30 to 60 mL/min). The steady-state trough concentrations in these two groups were similar to those in patients with normal renal function (CLcr greater than 90 mL/min) in Studies A and B. No data are available in patients with severe and end-stage renal disease. Therefore, no formal dosing recommendation could be made.

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

Elderly :
Clinical studies of XALKORI did not include sufficient numbers of patients aged 65 years or older to determine whether they respond differently from younger patients. Of the 125 patients in Study A, 18 (14%) were 65 years or older. Of the 261 patients in Study B, 30 (11 %) were 65 years or older. Considering the limited data available in this subgroup of patients, no formal dosing recommendation can be made until additional data become available.

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

Hepatotoxicity

Drug-induced hepatotoxicity with fatal outcome has occurred. These cases have occurred during XALKORI treatment in less than 1% of patients in clinical trials. Concurrent elevations in ALT greater than 3 x ULN and total bilirubin greater than 2 x ULN without elevated alkaline phosphatase have been observed in less than 1% patients in clinical trials. Increases to Grade 3 or 4 ALT elevation were observed in 4% of patients in Study A and 7% of patients in Study B. Grade 3 and 4 elevations were generally asymptomatic and reversible upon dosing interruption. Patients usually resumed treatment at a lower dose without recurrence; however, 1 patient from Study A (<1%) and 3 patients from Study B (2%) required permanent discontinuation from treatment. Transaminase elevations generally occurred within the first 2 months of treatment. Liver function tests including ALT and total bilirubin should be monitored once a month and as clinically indicated, with more frequent repeat testing for Grades 2, 3 or 4 elevation. For patients who develop transaminase elevations, see **Dose Modification** section (see Section **Posology and method of administration).**

Pneumonitis

Crizotinib has been associated with severe, life-threatening, or fatal treatment-related pneumonitis in clinical trials with a frequency of 4 in 255 (1.6%) patients across Studies A and B. All of these cases occurred within 2 months after the initiation of treatment. Patients should be monitored for pulmonary symptoms indicative of pneumonitis. Other causes of pneumonitis should be excluded. Crizotinib should be permanently discontinued in patients diagnosed with treatment-related 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 diarrhoea 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 Section **Posology and method of administration and Pharmacokinetics properties**).

Visual effects

Vision disorder occurred in patients in Study A and Study B. Ophthalmological evaluation should be considered if vision disorder persists or worsens in severity.

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

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

Coadministration 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. Coadministration of crizotinib with strong CYP3A inducers may decrease crizotinib plasma concentrations. The concurrent use of strong CYP3A inducers, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, 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, coadministration 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.

Coadministration of crizotinib and antacids

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

Fertility, Pregnancy and Lactation

Contraception in males and females

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

Pregnancy

XALKORI may cause fetal harm when administered to a pregnant woman. Studies in animals have shown reproductive toxicity.
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

Data described below reflect exposure to XALKORI in 386 patients with previously treated ALK-positive NSCLC who participated in 2 single-arm clinical trials (Studies A and B). These patients received a starting oral dose of 250 mg taken twice daily continuously. Comparative safety data from randomized clinical trials are not yet available.

Tabulated list of adverse reactions

Table 3 lists the incidences of adverse reactions commonly reported in patients receiving XALKORI. Most adverse reactions were Grade 1 or 2 in severity. The most common any grade adverse reactions (>20%) across both studies were vision disorder, nausea, diarrhoea, vomiting, oedema, constipation, and fatigue. The most common Grade 3 or 4 adverse reactions (≥3%) across both studies were increased ALT and neutropenia. The potentially serious adverse reactions of pneumonitis and QT interval prolongation are described in section 4.4. Dose reductions associated with adverse events occurred in 6% of patients in Study A and 15% of patients in Study B. The rates of treatment-related adverse events resulting in permanent discontinuation were 2% in Study A and 4% in Study B.

Note: Frequency categories are defined using the following convention: very common (>1/10), common (>1/100 to <1/10), uncommon (>1/1000 to <1/100), rare (>1/10,000 to <1/1000), very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3. Adverse Reactions Reported in Studies A[a] and B[a]

Adverse Reaction, n (%)	**Frequency[b]**	**(N=386)**	
		All Grades	Grade 3/4
Blood and lymphatic system disorders			
Neutropenia	Very Common	39 (10)	26 (7)
Leukopenia	Common	17 (4)	2 (<1)
Lymphopenia	Common	9 (2)	8 (2)
Anemia	Common	6 (2)	1 (<1)
Metabolism and nutrition disorders			
Decreased Appetite	Very Common	73 (19)	0 (0)
Hypophosphatemia	Common	10 (3)	6 (2)
Nervous system disorders			
Neuropathy[c]	Very Common	44 (11)	2 (<1)
Dizziness	Very Common	59 (15)	0 (0)
Dysgeusia	Very Common	51 (13)	0 (0)
Eye disorders			
Vision Disorder[c]	Very Common	225 (58)	1 (<1)
Cardiac disorders			
Bradycardia[c]	Common	14 (4)	0 (0)
Respiratory, thoracic and mediastinal disorders			
Pneumonitis	Common	4 (1)	4 (1)[d]
Gastrointestinal disorders			
Vomiting	Very Common	157 (41)	3 (<1)
Nausea	Very Common	208 (54)	2 (<1)
Diarrhoea	Very Common	160 (42)	2 (<1)
Constipation	Very Common	111 (29)	0 (0)
Oesophageal-related disorder[c]	Common	24 (6)	0 (0)
Dyspepsia	Common	19 (5)	0 (0)
Skin and subcutaneous tissue disorders			
Rash	Common	35 (9)	0 (0)
Renal and urinary disorders			
Renal cyst[e]	Uncommon	2 (<1)	1 (<1)
General disorders and administration site conditions			
Fatigue[c]	Very Common	86 (22)	6 (2)
Oedema[c]	Very Common	104 (27)	0 (0)
Investigations			
Alanine aminotransferase increased	Very Common	53 (14)	20 (5)
Electrocardiogram QT prolonged	Common	4 (1)	2 (<1)
Aspartate aminotransferase increased	Common	38 (10)	7 (2)
Blood alkaline phosphatase increased	Common	9 (2)	0 (0)

[a]Study A used NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, and Study B used NCI CTCAE version 4.0

[b]Based on highest frequency between Study A and Study B

[c]Includes cases reported within the clustered terms: oedema (oedema, edema peripheral), oesophageal-related disorder (gastroesophageal reflux disease, odynophagia, oesophageal pain, oesophageal ulcer, oesophagitis, reflux oesophagitis, dysphagia, epigastric discomfort), neuropathy (neuralgia, neuropathy peripheral, paraesthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, sensory disturbance), vision disorder (diplopia, photopsia, vision blurred, visual impairment, vitreous floaters), bradycardia (bradycardia, sinus bradycardia), and fatigue (asthenia, fatigue)

[d]Includes 1 Grade 5 event.

[e]Includes complex renal cysts

Description of selected adverse reactions

Hepatotoxicity

Drug-induced hepatotoxicity with fatal outcome has occurred. These cases have occurred during XALKORI treatment in less than 1% of patients in clinical trials. Concurrent elevations in ALT greater than 3 x ULN and total bilirubin greater than 2 x ULN without elevated alkaline phosphatase have been observed in less than 1% patients in clinical trials. Increases to Grade 3 or 4 ALT elevation were observed in 6% of patients in Study A and 8% of patients in Study B. Grade 3 and 4 elevations were generally asymptomatic and reversible upon dosing interruption. Patients usually resumed treatment at a lower dose without recurrence; however, 1 patient from Study A (<1%) and 3 patients from Study B (1%) required permanent discontinuation from treatment. Transaminase elevations generally occurred within the first 2 months of treatment. XALKORI should not be used in patients with severe hepatic impairment. Liver function tests including ALT, AST, and total bilirubin should be monitored twice a month during the first 2 months of treatment, then once a month and as clinically indicated, with more frequent repeat testing for Grades 2, 3 or 4 elevation. For patients who develop transaminase elevation.

Visual Effects

Vision disorder including diplopia, photopsia, vision blurred, visual impairment, and vitreous floaters was experienced by 76 (61%) patients in Study A and 149 (57%) patients in Study B. This event was reported as mild (96%), moderate (3%), and severe (<1%) with median times to onset of 15 and 6 days in Studies A and B, respectively. None of the patients in Studies A and B required dose reduction, or permanent discontinuation from crizotinib treatment for vision disorder; however 1 patient in Study A and 3 patients in Study B had temporary treatment discontinuation. Ophthalmological evaluation should be considered if vision disorder persists or worsens in severity.

Gastrointestinal Effects

Nausea, diarrhoea, vomiting, and constipation were the most commonly reported gastrointestinal events, and were primarily Grade 1 in severity. Supportive care for

gastrointestinal events may include standard antiemetic and/or antidiarrhoeal or laxative medicinal products.

Nervous System Effects

Neuropathy as defined in Table 3, primarily peripheral neuropathy, was experienced by 11 (9%) patients in Study A and 33 (13%) patients in Study B, and was primarily Grade 1 in severity. Dizziness and dysgeusia were also very commonly reported in these studies, but were all Grades 1 or 2 in severity.

Laboratory Abnormalities/Testing

Transaminase elevation
Increases to Grade 3 or 4 ALT elevation was observed in 6% of patients in Study A and 8% of patients in Study B. Grades 3 and 4 elevations were generally asymptomatic and reversible upon dosing interruption. Patients usually resumed treatment at a lower dose without recurrence; however, 1 patient, from Study A (<1%) and 3 patients from Study B (1%) required permanent discontinuation from treatment. Concurrent elevations in ALT >3 x ULN and total bilirubin >2 x ULN without elevated alkaline phosphatase were detected in 1 out of 375 (<0.5%) of patients with available laboratory data across both studies. Liver function tests including ALT, AST, and total bilirubin should be monitored twice a month during the first 2 months of treatment, then once a month and as clinically indicated, with more frequent repeat testing for Grades 2, 3 or 4 elevation. For patients who develop transaminase elevations.

Hematologic Laboratory Abnormalities
In Study A, decreases to Grade 3 or 4 leukocytes and platelets were each observed in patients at frequencies of <3%, and decreases to Grade 3 or 4 neutrophils and lymphocytes were observed at a frequency of 10% and 14%, respectively. In Study B, decreases to Grade 3 or 4 leukocytes were observed in patients at a frequency of 3%, decreases to Grade 3 or 4 neutrophils were observed at a frequency of 9%, decreases to Grade 3 or 4 lymphocytes were observed at a frequency of 14%, and decreases to Grade 3 or 4 platelets were observed at a frequency of <1%. 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 section **Posology and method of administration**.

Overdose
There have been no known cases of crizotinib 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. Crizotinib demonstrated concentration-dependent inhibition of the kinase activity of ALK 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 EML4-ALK and 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.*

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 7 times human clinical exposure based on AUC). Other toxicities of potential concern to pediatric patients have not been evaluated in juvenile animals.

Clinical studies

The use of single-agent XALKORI in the treatment of ALK-positive advanced NSCLC was investigated in 2 multicenter, single-arm studies (Studies A [A8081001] and B [A8081005]). Of the patients enrolled in these studies, the patients described below had received prior systemic therapy for locally advanced or metastatic disease. The primary efficacy endpoint in both studies was Objective Response Rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST). Secondary endpoints included Time to Tumor Response (TTR), Duration of Response (DR), Disease Control Rate (DCR), Progression-Free Survival (PFS), and Overall Survival (OS). Comparative efficacy data from randomized clinical trials are not yet available.

Patients received 250 mg of crizotinib orally twice daily. Demographic and disease characteristics for Studies A and B are provided in Table 4.

Table 4. Demographic and Disease Characteristics in Studies A and B

Characteristics	Study A N=125	Study B N=261
Sex, n (%)		
Male	63 (50)	119 (46)
Female	62 (50)	142 (54)
Age (years), n (%)		
Median (range)	51 (21-79)	52 (24-82)
<65 years	107 (86)	231 (89)
≥65 years	18 (14)	30 (11)
Race, n (%)		
White	76 (61)	152 (58)
Black	5 (4)	8 (3)
Asian	37 (30)	96 (37)
Other	7 (6)	5 (2)
Smoking status, n (%)		
Never smoked	90 (72)	176 (67)
Former smoker	34 (27)	73 (28)
Current smoker	1 (1)	12 (5)
Disease Stage		
Locally advanced	7 (6)	21 (8)
Metastatic	118 (94)	240 (92)
Histological classification		
Adenocarcinoma	122 (98)	242 (93)
Large cell carcinoma	1 (1)	4 (2)
Squamous cell carcinoma	1 (1)	3 (1)
Adenosquamous carcinoma	0 (0)	3 (1)
Other	1 (1)	9 (3)
ECOG PS at baseline, n (%)		
0	40 (32)	67 (26)
1	69 (55)	147 (56)
2-3[a]	16 (13)	47 (18)
Prior Radiation Therapy		
No	51 (41)	107 (41)
Yes	74 (59)	153 (59)
Not Reported	0 (0)	1 (1)
Prior Systemic Therapy for Advanced Disease Number of Advanced/Metastatic Regimens		
0	0 (0)	0 (0)
1	47 (38)	27 (10)
2	31 (25)	90 (35)
≥3	47 (38)	144 (55)

[a]Includes 1 patient with an ECOG PS of 1 at screening but was 3 at baseline.

In Study A, 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 twenty-five patients with previously treated ALK-positive advanced NSCLC were enrolled into Study A at the time of data cut off. The median duration of treatment was 42 weeks.

In Study B, patients with advanced NSCLC were required to have ALK-positive tumors prior to entering the clinical trial. ALK-positive NSCLC was identified using the Vysis ALK Break-Apart FISH Probe Kit assay.

Two hundred sixty-one patients with previously treated ALK-positive advanced NSCLC from Study B were analyzed at the time of data cut off. The median duration of treatment was 25 weeks.

Main efficacy data from Studies A and B are provided in Table 5 .

Table 5. ALK-Positive Advanced NSCLC Efficacy Results from Studies A and B

Efficacy Parameter	**Study A (N=125)**	**Study B (N=261)**
Objective Response Rate[a] [% (95% CI)]	**60% (51%, 69%)**	**53% (47%, 60%)**
Time to Tumour Response [median (range)]	7.9 weeks (2.1 weeks, 39.6 weeks)	6.1 weeks (4.9 weeks, 30.4 weeks)
Duration of Response[b] [median (95% CI)]	**48.1 weeks (35.7 weeks, 64.1 weeks)**	**42.9 weeks (36.1 weeks, 49.7 weeks)**
Disease Control Rate[c] at 8 weeks (Study A) [% (95% CI)]; at 6 weeks (Study B) [% (95% CI)]	84% (77%, 90%)	85% (80%, 89%)
Progression Free Survival[b] [median (95% CI)]	**9.2 months (7.3 months, 12.7 months)**	**8.5 months (6.5 months, 9.9 months)**
Median OS	Not reached	Not reached
OS probability at 12 months[b] [% (95% CI)]	72% (63%, 80%)	61% (49%, 71%)

[a] Four patients were not evaluable for response in Study A and 6 patients were not evaluable for response in Study B

[b] Estimated using the Kaplan-Meier method

[c] Proportion of patients with a RECIST-defined complete response, partial response, or stable disease at 8 weeks (Study A) or at 6 weeks (Study B)

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 AUC_{inf} and 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 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

Coadministration 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 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).**

Coadministration of Crizotinib and CYP3A Inhibitors
Coadministration of a single 150 mg oral dose of crizotinib in the presence of ketoconazole (200 mg twice daily), a strong CYP3A inhibitor, resulted in increases in crizotinib systemic exposure, with crizotinib AUC_{inf} and C_{max} values that were approximately 3.2-fold and 1.4-fold, respectively, those seen when crizotinib was administered alone. However, the magnitude of effect of CYP3A inhibitors on steady-state crizotinib exposure has not been established (see Section **Interaction with other medicinal products and other forms of interaction**).

Coadministration of Crizotinib and CYP3A Inducers
Coadministration of a single 250 mg crizotinib dose with rifampin (600 mg QD), a strong CYP3A inducer, resulted in 82% and 69% decreases in crizotinib AUC_{inf} and C_{max}, respectively, compared to when crizotinib was given alone. However, the effect of CYP3A inducers on steady-state crizotinib exposure has not been established (see Section **Interaction with other medicinal products and other forms of interaction**).

Coadministration of Crizotinib and Antacids
The aqueous solubility of crizotinib is pH dependent, with low (acidic) pH resulting in higher solubility. In general, 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. The use of antacids was permitted during crizotinib treatment in patient trials. Based on population PK modeling, coadministration of antacids is unlikely to result in changes in steady state crizotinib exposure, However, no formal studies have been conducted.

Coadministration with other CYP Substrates
In vitro studies indicated that clinical drug-drug interactions are unlikely to occur as a result of crizotinib-mediated inhibition of the metabolism of drugs that are substrates for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP2D6.

An *in vitro* study in human hepatocytes indicated that clinical drug-drug interactions are unlikely to occur as a result of crizotinib-mediated induction of the metabolism of drugs that are substrates for CYP1A2 or CYP3A.

Coadministration 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 coadministered drugs that are substrates of P-gp.

In vitro, crizotinib did not inhibit the human hepatic uptake transport proteins OATP1B1 or OATP1B3 at therapeutic concentrations. Therefore, clinical drug-drug interactions are

unlikely to occur as a result of crizotinib-mediated inhibition of the hepatic uptake of drugs that are substrates for these transporters.

Pharmacokinetics in special patient groups

Hepatic Insufficiency: Crizotinib has not been studied in patients with hepatic impairment. Clinical studies that were conducted excluded patients with ALT or AST >2.5 x ULN or, if due to underlying malignancy, >5.0 x ULN or with total bilirubin >1.5 x ULN.

Renal Insufficiency: No starting dose adjustment is recommended for patients with mild (creatinine clearance [CLcr] 60 to 90 mL/min) and moderate renal impairment (CLcr 30 to 60 mL/min). The steady-state trough concentrations in these two groups were similar to those in patients with normal renal function (CLcr greater than 90 mL/min) in Studies A and B. No data are available in patients with severe and end-stage renal disease. Therefore, no formal dosing recommendation could be made.

Ethnicity: After 250 mg twice daily dosing, steady-state crizotinib C_{max} and AUC_{τ} in Asian patients were 1.57 - (90% CI: 1.16-2.13) and 1.50 - (90% CI: 1.10-2.04) fold those seen in non-Asian patients, respectively.

Cardiac electrophysiology

The QT interval prolongation potential of crizotinib was assessed in all patients 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. Four of 382 patients (1.0%) were found to have QTcF (corrected QT by the Fridericia method) ≥500 msec, and 15 of 364 patients (4.1%) had an increase from baseline QTcF ≥60 msec by automated machine-read evaluation of ECG. A central tendency analysis of the QTcF data demonstrated that the highest upper bound of the two-sided 90% Cl for QTcF was <15 msec at the protocol pre-specified time points. A pharmacokinetic/pharmacodynamic analysis suggested a relationship between crizotinib plasma concentration and QTc.

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 AUG. 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 2-fold 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. Postimplantation 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 2-fold 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 6 blister @ 10 capsules
XALKORI® 200 mg ; Box of 1 HDPE bottle @ 60 capsules

XALKORI® 250 mg ; Box of 6 blister @ 10 capsules
XALKORI® 250 mg ; Box of 1 HDPE bottle @ 60 capsules

Store below 30°C

Manufactured by
Pfizer Manufacturing Deutschland GmbH,
Freiburg, Germany.

Imported by :
PT. Pfizer Indonesia
PO Box 2706
Jakarta,
Indonesia

Leaflet kemasan: Informasi bagi pengguna
XALKORI 200 mg kapsul
XALKORI 250 mg kapsul
Crizotinib

Bacalah seluruh isi leaflet ini dengan seksama 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 jenis kanker paru yang disebut kanker paru jenis karsinoma bukan sel-kecil (KPKBSK), yang muncul dengan penyusunan ulang atau kerusakan spesifik dalam gen yang disebut limfoma kinase anaplastik (ALK).

XALKORI dapat diresepkan jika penyakit Anda berada pada stadium lanjut dan pengobatan terdahulu tidak mampu membantu menghentikan penyakit Anda.

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

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 Daftar Zat Tambahan/ *List of Exipients)*, maka jangan meminum obat ini.
- Jika Anda mengidap penyakit hati yang parah.

Peringatan dan kehati-hatian

Konsultasikan dengan dokter Anda sebelum meminum XALKORI:

- Jika Anda mengidap 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-gejalanva 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 memiliki gangguan penglihatan (melihat kilatan cahaya, penglihatan yang kabur, dan penglihatan ganda).
- Jika saat ini Anda dirawat dengan salah satu obat yang tercantum dalam bagian ***Obat-obatan lain dan XALKORI.***

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 tersebut 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 jika digunakan secara bersamaan:

- 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 memberikan peningkatan efek samping dari obat-obat berikut ini jika digunakan secara bersamaan:
- 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.

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 tidak akan berfungsi efektif.

Antasida
Jika Anda meminum XALKORI bersamaan obat-obat yang dapat meningkatkan keasaman lambung (seperti golongan penghambat pompa proton, H_2 bloker, atau antasida), maka kemungkinan akan menurunkan kelarutan XALKORI dan mengurangi ketersediaanya dalam tubuh Anda.

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

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 menjalankan mesin
Anda harus sangat berhati-hati saat mengemudi dan menjalankan 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 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 jeruk bali.
- 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.

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

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

- Jika jarak dosis Anda berikutnya adalah dalam waklu **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 “Apa yang perlu Anda ketahui sebelum meminum XALKORI”):

- Fungsi hati abnormal

Segera beri tahu dokter jika Anda merasa lelah berlebihan dari biasanya, kulit dan bagian putih pada mata berubah menjadi kuning, air seni menjadi gelap atau cokelat (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.

- 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.

Efek samping lain dari XALKORI dapat meliputi:
Efek samping yang sangat umum (dapat dialami oleh lebih dari 1 orang dari 10 pasien)

- Abnormalitas dalam tes darah dan hati.
- Gangguan penglihatan (melihat kilatan cahaya, penglihatan kabur, atau penglihatan ganda, sering dimulai tidak lama setelah memulai pengobatan dengan XALKORI).
- Neuropati (perasaan kebas atau seperti tertusuk pada persendian, tangan dan kaki, atau otot).
- Pusing.
- Kelelahan.
- Edema (cairan berlebih di dalam jaringan tubuh, sehingga menyebabkan pembengkakan tangan dan kaki).
- Gangguan perut, termasuk mual, muntah, diare, konstipasi, dan gangguan esofagus (tenggorokan).
- Penurunan nafsu makan.
- Perubahan ketajaman indera perasa/pengecap.
- Ruam kulit.

Efek samping yang umum (dapat dialami oleh 1 hingga 10 orang dari 100 pasien)

- Penurunan jumlah sel darah merah (anemia), sel darah putih (yang penting dalam memerangi infeksi) dan trombosit (yang penting untuk pembekuan darah).
- Gangguan pencernaan.
- Penurunan denyut jantung.

Efek samping yang tidak umum (dapat dialami oleh 1 hingga 10 orang dari 1000 pasien)

- Terbentuknya kantung-kantung cairan tertutup di dalam ginjal (kista ginjal kompleks).

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
- Obat ini tidak mengharuskan kondisi penyimpanan khusus
- 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.

XALKORI 200 mg: setiap kapsul mengandung 200 mg crizotinib
XALKORI 250 mg: setiap kapsul mengandung 250 mg crizotinib

- Bahan-bahan lainnya adalah:

Isi kapsul: silika, koloidal anhidrat, selulosa mikrokristal, kalsium hidrogen fosfat, anhidrat, natrium pati glikolat (Tipe A), magnesium stearat.
Cangkang kapsul: gelatin, titanium dioksida (E171), dan besi oksida merah (E172).
Tinta printing: shellac, propilen glikol, 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, "CRZ200" 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 60 kapsul dan dalam botol plastik berisi 60 kapsul.

Tidak semua ukuran kemasan tersedia di pasaran.

Pemegang Izin Pemasaran

PT Pfizer Indonesia
PO Box 2706
Jakarta, INDONESIA

Produsen

Pfizer Manufacturing Deutschland GmbH,
Freiburg, Jerman