ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

XALKORI 200 mg hard capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 200 mg of crizotinib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

White opaque and pink opaque hard capsule, with “Pfizer” imprinted on the cap and “CRZ 200” on the body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Treatment with XALKORI should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

ALK testing

An accurate and validated ALK assay is necessary for the selection of patients for treatment with XALKORI (see section 5.1 for information on assays used in the trials).

Assessment for ALK-positive NSCLC should be performed by laboratories with demonstrated proficiency in the specific technology being utilised.

Posology

The recommended dose schedule of XALKORI is 250 mg twice daily (500 mg daily) taken continuously. Treatment should be continued until disease progression or unacceptable toxicity. Prolongation of treatment after objective disease progression in selected patients may be considered on an individual basis, but no additional benefit has been demonstrated.

If a dose 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 adjustments

Dosing interruption and/or dose reduction may be required based on individual safety and tolerability. If dose reduction is necessary, then the dose of XALKORI should be reduced to 200 mg taken twice daily. If further dose reduction is necessary, then the dose should be modified to 250 mg taken once

daily based on individual safety and tolerability. Dose reduction guidelines for hematologic and non-hematologic toxicities are provided in Tables 1 and 2.

Table 1. XALKORI dose modification – Hematologic toxicities[a]

CTCAE[b] Grade	XALKORI treatment
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
[b]National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events
[c]In case of recurrence, dosing should be withheld until recovery to Grade ≤2, then dosing should be resumed at 250 mg once daily. XALKORI must be permanently discontinued in case of further Grade 4 recurrence.

Table 2. XALKORI dose modification – Non-hematologic toxicities

CTCAE[a] Grade	XALKORI treatment
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, dosing should be withheld until recovery to Grade ≤1, then dosing should be resumed at 250 mg once daily. XALKORI must be permanently discontinue in case of further Grade 3 or 4 recurrence.
[c]Not attributable to NSCLC progression, other pulmonary disease, infection, or radiation effect. XALKORI should be withheld if pneumonitis is suspected, and must be permanently discontinued if treatment-related pneumonitis is diagnosed.

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 (see Table 2 and section 4.8). XALKORI should not be used in patients with severe hepatic impairment, see section 4.3.

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 (see section 5.2). Therefore, no formal dosing recommendation could be made.

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 (see

section 5.2). Considering the limited data available in this subgroup of patients, no formal dosing recommendation can be made until additional data become available.

Paediatric population

The safety and efficacy of XALKORI in paediatric patients has not been established. No data are available.

Method of administration

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 (see section 4.5).

4.3 Contraindications

Hypersensitivity to crizotinib or to any of the excipients listed in section 6.1.

Severe hepatic impairment (see sections 4.2, 4.4, and 4.8).

4.4 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 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 (see sections 4.2, 4.3, and 4.8). 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, see section 4.2.

Pneumonitis

XALKORI has been associated with severe, life-threatening, or fatal treatment-related pneumonitis in clinical trials with a frequency of 4 in 386 (1%) patients across Studies A and B. All of these cases occurred within 2 months after the initiation of treatment. Patients with pulmonary symptoms indicative of pneumonitis should be monitored. XALKORI treatment should be withheld if pneumonitis is suspected. Other causes of pneumonitis should be excluded, and XALKORI should be permanently discontinued in patients diagnosed with treatment-related pneumonitis (see section 4.2).

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 4.2.

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 (see section 4.8).

Drug-drug interactions

The concomitant use of crizotinib with strong CYP3A4 inhibitors/inducers and CYP3A4 substrates with narrow therapeutic indices should be avoided (see section 4.5).

Elderly

Limited information is available in patients ≥65 years old, and there is no information in patients over 85 years of age.

Non-adenocarcinoma histology

Limited information is available in patients with ALK-positive NSCLC with non-adenocarcinoma histology. The clinical benefit may be lower in this subpopulation, which should be taken into account before individual treatment decisions are made (see section 5.1).

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

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 4.2 and 4.4). 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 4.4). 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 4.4). 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.

Pharmacodynamic interactions

In clinical studies, prolonged QT interval was observed with crizotinib. Therefore, the concomitant use of crizotinib with medicinal products known to prolong QT interval or medicinal products able to induce Torsades de pointes (e.g., class IA [quinidine, disopyramide] or class III [e.g., amiodarone, sotalol, dofetilide, ibutilide], methadone, cisapride, moxifloxacine, antipsychotics, etc.) should be carefully considered. A monitoring of the QT interval should be made in case of combinations of such medicinal products (see section 4.4).

Bradycardia has been reported during clinical studies; therefore, use crizotinib with caution due to the risk of excessive bradycardia when used in combination with other bradycardic agents (e.g., non-dihydropyridine calcium channel blockers such as verapamil and diltiazem, beta-blockers, clonidine, guanfacine, digoxin, mefloquine, anticholinesterases, pilocarpine).

4.6 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 (see section 4.5).

Pregnancy

XALKORI may cause fetal harm when administered to a pregnant woman. Studies in animals have shown reproductive toxicity (see section 5.3).

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 a 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 (see section 5.3).

Fertility

Based on nonclinical safety findings, male and female fertility may be compromised by treatment with XALKORI (see section 5.3). Both men and women should seek advice for fertility preservation before treatment.

4.7 Effects on ability to drive and use machines

XALKORI has minor influence on the ability to drive and use machines. However, caution should be exercised when driving or operating machines as patients may experience vision disorder, dizziness, or fatigue while taking XALKORI (see section 4.8).

4.8 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, oedema 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 (see sections 4.2, 4.3, 4.4). 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, see section 4.2.

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 (see section 4.2).

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, see section 4.2.

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 4.2.

4.9 Overdose

There have been no known cases of XALKORI overdose. Treatment of overdose with the medicinal product consists of general supportive measures. There is no antidote for XALKORI.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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 tumour cell lines exhibiting ALK fusion events (including EML4-ALK and NPM-ALK) or exhibiting amplification of the *ALK* or *MET* gene locus. Crizotinib demonstrated anti-tumour efficacy, including marked cytoreductive anti-tumour activity, in mice bearing tumour xenografts that expressed ALK fusion proteins. The anti-tumour efficacy of crizotinib was dose-dependent and correlated to pharmacodynamic inhibition of phosphorylation of ALK fusion proteins (including EML4-ALK and NPM-ALK) in tumours *in vivo*.

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 Tumours (RECIST). Secondary endpoints included Time to Tumour 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 tumours 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 cutoff. The median duration of treatment was 42 weeks.

In Study B, patients with advanced NSCLC were required to have ALK-positive tumours 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 cutoff. 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)

Non-adenocarcinoma histology
Information is available from only 29 response-evaluable patients with non-adenocarcinoma NSCLC in Studies A and B. Partial responses were observed in 10 of these patients for an ORR of 31%, which was less than the ORRs reported in Study A (60%) and Study B (53%). Comparisons with ORR in this subgroup of NSCLC patients treated with standard chemotherapy are not yet available (see section 4.4).

Elderly

Clinical studies of XALKORI did not include sufficient numbers of patients aged 65 years and 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. No patients in Studies A or B were 85 years or older.

Patients with brain metastases

Twenty patients in Study B were enrolled with asymptomatic brain metastases that were not irradiated, 17 of whom were evaluable for both brain metastasis and systemic tumour responses. Eight (47%) of these 17 patients had responses in the brain that matched or exceeded the systemic tumour responses, 2 (25%) of whom had complete brain metastasis responses. Nine (53%) of these 17 patients had systemic tumour responses that exceeded the brain metastasis responses, 8 (89%) of whom had stable brain disease for at least 3 tumour reassessments.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with XALKORI in all subsets of the paediatric population in NSCLC. Lung carcinoma is included under the list of conditions waived for paediatric development since this condition does not normally occur in the paediatric population (see section 4.2 for information on paediatric use).

Conditional approval

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited, including the results of a comparative study versus standard chemotherapy (pemetrexed or docetaxel) in the indication. The European Medicines Agency will review new information on this medicinal product at least every year, and this SmPC will be updated as necessary.

5.2 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. With twice daily dosing, steady-state was achieved within 15 days. The absolute bioavailability of crizotinib was determined to be 43% 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 2.1).

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 medicinal product concentration. *In vitro* studies suggest that crizotinib is a substrate for P-glycoprotein (P-gp).

Biotransformation

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 (see section 4.5). *In vitro* studies indicated that clinical drug-drug interactions are unlikely to occur as a result of crizotinib-mediated inhibition of the metabolism of medicinal products 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 medicinal products that are substrates for CYP1A2 or CYP3A. However, the possibility of crizotinib-mediated induction of other pregnane X receptor (PXR)-regulated enzymes (e.g., CYP2B6, CYP2C8, CYP2C9, UGT1A1) cannot be ruled out (see section 4.5).

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.

Coadministration with medicinal products 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 medicinal products that are substrates of P-gp (see section 4.5).

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 medicinal products 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 (see section 4.2).

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 (see section 4.2).

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.

Geriatric

Limited data are available in this subgroup of patients (see section 4.2, 4.4, 5.1). The effect of age on crizotinib pharmacokinetics has not been formally evaluated.

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% CI 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 (see section 4.4).

5.3 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 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Silica, colloidal anhydrous
Cellulose, microcrystalline
Calcium hydrogen phosphate, anhydrous
Sodium starch glycolate (Type A)
Magnesium stearate

Capsule shell
Gelatin
Titanium dioxide (E171)
Red iron oxide (E172)

Printing ink
Shellac
Propylene glycol
Potassium hydroxide
Black iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

HDPE bottles with a polypropylene closure containing 60 hard capsules.

PVC-foil blisters containing 10 hard capsules.

Each carton contains 60 hard capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

XALKORI 250 mg hard capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 250 mg of crizotinib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

Pink opaque hard capsule, with “Pfizer” imprinted on the cap and “CRZ 250” on the body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Treatment with XALKORI should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

ALK testing

An accurate and validated ALK assay is necessary for the selection of patients for treatment with XALKORI (see section 5.1 for information on assays used in the trials).

Assessment for ALK-positive NSCLC should be performed by laboratories with demonstrated proficiency in the specific technology being utilised.

Posology

The recommended dose schedule of XALKORI is 250 mg twice daily (500 mg daily) taken continuously. Treatment should be continued until disease progression or unacceptable toxicity. Prolongation of treatment after objective disease progression in selected patients may be considered on an individual basis, but no additional benefit has been demonstrated.

If a dose 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 adjustments

Dosing interruption and/or dose reduction may be required based on individual safety and tolerability. If dose reduction is necessary, then the dose of XALKORI should be reduced to 200 mg taken twice daily. If further dose reduction is necessary, then the dose should be modified to 250 mg taken once

daily based on individual safety and tolerability. Dose reduction guidelines for hematologic and non-hematologic toxicities are provided in Tables 1 and 2.

Table 1. XALKORI dose modification – Hematologic toxicities[a]

CTCAE[b] Grade	XALKORI treatment
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
[b]National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events
[c]In case of recurrence, dosing should be withheld until recovery to Grade ≤2, then dosing should be resumed at 250 mg once daily. XALKORI must be permanently discontinued in case of further Grade 4 recurrence.

Table 2. XALKORI dose modification – Non-hematologic toxicities

CTCAE[a] Grade	XALKORI treatment
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, dosing should be withheld until recovery to Grade ≤1, then dosing should be resumed at 250 mg once daily. XALKORI must be permanently discontinued in case of further Grade 3 or 4 recurrence.
[c]Not attributable to NSCLC progression, other pulmonary disease, infection, or radiation effect. XALKORI should be withheld if pneumonitis is suspected, and must be permanently discontinued if treatment-related pneumonitis is diagnosed.

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 (see Table 2 and section 4.8). XALKORI should not be used in patients with severe hepatic impairment, see section 4.3.

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 (see section 5.2). Therefore, no formal dosing recommendation could be made.

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 (see

section 5.2). Considering the limited data available in this subgroup of patients, no formal dosing recommendation can be made until additional data become available.

Paediatric population

The safety and efficacy of XALKORI in paediatric patients has not been established. No data are available.

Method of administration

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 (see section 4.5).

4.3 Contraindications

Hypersensitivity to crizotinib or to any of the excipients listed in section 6.1.

Severe hepatic impairment (see sections 4.2, 4.4, and 4.8).

4.4 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 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 (see sections 4.2, 4.3, and 4.8). 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, see section 4.2.

Pneumonitis

XALKORI has been associated with severe, life-threatening, or fatal treatment-related pneumonitis in clinical trials with a frequency of 4 in 386 (1%) patients across Studies A and B. All of these cases occurred within 2 months after the initiation of treatment. Patients with pulmonary symptoms indicative of pneumonitis should be monitored. XALKORI treatment should be withheld if pneumonitis is suspected. Other causes of pneumonitis should be excluded, and XALKORI should be permanently discontinued in patients diagnosed with treatment-related pneumonitis (see section 4.2).

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 4.2.

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 (see section 4.8).

Drug-drug interactions

The concomitant use of crizotinib with strong CYP3A4 inhibitors/inducers and CYP3A4 substrates with narrow therapeutic indices should be avoided (see section 4.5).

Elderly

Limited information is available in patients ≥65 years old, and there is no information in patients over 85 years of age.

Non-adenocarcinoma histology

Limited information is available in patients with ALK-positive NSCLC with non-adenocarcinoma histology. The clinical benefit may be lower in this subpopulation, which should be taken into account before individual treatment decisions are made (see section 5.1).

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

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 4.2 and 4.4). 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 4.4). 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 4.4). 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.

Pharmacodynamic interactions

In clinical studies, prolonged QT interval was observed with crizotinib. Therefore, the concomitant use of crizotinib with medicinal products known to prolong QT interval or medicinal products able to induce Torsades de pointes (e.g., class IA [quinidine, disopyramide] or class III [e.g., amiodarone, sotalol, dofetilide, ibutilide], methadone, cisapride, moxifloxacine, antipsychotics, etc.) should be carefully considered. A monitoring of the QT interval should be made in case of combinations of such medicinal products (see section 4.4).

Bradycardia has been reported during clinical studies; therefore, use crizotinib with caution due to the risk of excessive bradycardia when used in combination with other bradycardic agents (e.g., non-dihydropyridine calcium channel blockers such as verapamil and diltiazem, beta-blockers, clonidine, guanfacine, digoxin, mefloquine, anticholinesterases, pilocarpine).

4.6 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 (see section 4.5).

Pregnancy

XALKORI may cause fetal harm when administered to a pregnant woman. Studies in animals have shown reproductive toxicity (see section 5.3).

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 a 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 (see section 5.3).

Fertility

Based on nonclinical safety findings, male and female fertility may be compromised by treatment with XALKORI (see section 5.3). Both men and women should seek advice for fertility preservation before treatment.

4.7 Effects on ability to drive and use machines

XALKORI has minor influence on the ability to drive and use machines. However, caution should be exercised when driving or operating machines as patients may experience vision disorder, dizziness, or fatigue while taking XALKORI (see section 4.8).

4.8 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, oedema 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 (see sections 4.2, 4.3, 4.4). 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, see section 4.2.

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 (see section 4.2).

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, see section 4.2.

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 4.2.

4.9 Overdose

There have been no known cases of XALKORI overdose. Treatment of overdose with the medicinal product consists of general supportive measures. There is no antidote for XALKORI.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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 tumour cell lines exhibiting ALK fusion events (including EML4-ALK and NPM-ALK) or exhibiting amplification of the *ALK* or *MET* gene locus. Crizotinib demonstrated anti-tumour efficacy, including marked cytoreductive anti-tumour activity, in mice bearing tumour xenografts that expressed ALK fusion proteins. The anti-tumour efficacy of crizotinib was dose-dependent and correlated to pharmacodynamic inhibition of phosphorylation of ALK fusion proteins (including EML4-ALK and NPM-ALK) in tumours *in vivo*.

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 Tumours (RECIST). Secondary endpoints included Time to Tumour 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 tumours 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 cutoff. The median duration of treatment was 42 weeks.

In Study B, patients with advanced NSCLC were required to have ALK-positive tumours 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 cutoff. 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)

Non-adenocarcinoma histology

Information is available from only 29 response-evaluable patients with non-adenocarcinoma NSCLC in Studies A and B. Partial responses were observed in 10 of these patients for an ORR of 31%, which was less than the ORRs reported in Study A (60%) and Study B (53%). Comparisons with ORR in this subgroup of NSCLC patients treated with standard chemotherapy are not yet available (see section 4.4).

Elderly

Clinical studies of XALKORI did not include sufficient numbers of patients aged 65 years and 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. No patients in Studies A or B were 85 years or older.

Patients with brain metastases

Twenty patients in Study B were enrolled with asymptomatic brain metastases that were not irradiated, 17 of whom were evaluable for both brain metastasis and systemic tumour responses. Eight (47%) of these 17 patients had responses in the brain that matched or exceeded the systemic tumour responses, 2 (25%) of whom had complete brain metastasis responses. Nine (53%) of these 17 patients had systemic tumour responses that exceeded the brain metastasis responses, 8 (89%) of whom had stable brain disease for at least 3 tumour reassessments.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with XALKORI in all subsets of the paediatric population in NSCLC. Lung carcinoma is included under the list of conditions waived for paediatric development since this condition does not normally occur in the paediatric population (see section 4.2 for information on paediatric use).

Conditional approval

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited, including the results of a comparative study versus standard chemotherapy (pemetrexed or docetaxel) in the indication. The European Medicines Agency will review new information on this medicinal product at least every year, and this SmPC will be updated as necessary.

5.2 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. With twice daily dosing, steady-state was achieved within 15 days. The absolute bioavailability of crizotinib was determined to be 43% 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 2.1).

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 medicinal product concentration. *In vitro* studies suggest that crizotinib is a substrate for P-glycoprotein (P-gp).

Biotransformation

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 (see section 4.5). *In vitro* studies indicated that clinical drug-drug interactions are unlikely to occur as a result of crizotinib-mediated inhibition of the metabolism of medicinal products 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 medicinal products that are substrates for CYP1A2 or CYP3A. However, the possibility of crizotinib-mediated induction of other pregnane X receptor (PXR)-regulated enzymes (e.g., CYP2B6, CYP2C8, CYP2C9, UGT1A1) cannot be ruled out (see section 4.5).

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.

Coadministration with medicinal products 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 medicinal products that are substrates of P-gp (see section 4.5).

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 medicinal products 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 (see section 4.2).

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 (see section 4.2).

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.

Geriatric

Limited data are available in this subgroup of patients (see section 4.2, 4.4, 5.1). The effect of age on crizotinib pharmacokinetics has not been formally evaluated.

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% CI 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 (see section 4.4).

5.3 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 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Silica, colloidal anhydrous
Cellulose, microcrystalline
Calcium hydrogen phosphate, anhydrous
Sodium starch glycolate (Type A)
Magnesium stearate

Capsule shell
Gelatin
Titanium dioxide (E171)
Red iron oxide (E172)

Printing ink
Shellac
Propylene glycol
Potassium hydroxide
Black iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

HDPE bottles with a polypropylene closure containing 60 hard capsules.

PVC-foil blisters containing 10 hard capsules.

Each carton contains 60 hard capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Pfizer Manufacturing Deutschland GmbH
Mooswaldallee 1
79090 Freiburg
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance presented in Module 1.8.1. of the Marketing Authorisation is in place and functioning before and whilst the medicinal product is on the market.

Risk Management Plan (RMP)
The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Prior to launch of the product in each Member State, the Marketing Authorisation Holder (MAH) shall agree the content and format of the educational material with the National Competent Authority. The final wording used on the educational material should be in line with the approved product information.

The MAH should ensure that, at launch and thereafter, all Healthcare Professionals who are expected to use and/or prescribe XALKORI are provided with an educational pack.

The educational pack should contain the following:

1. Summary of Product Characteristics and Package Leaflet.
2. Educational material for Healthcare Professionals.

3. Patient brochure including a Patient Alert Card (text as agreed by the CHMP).

The educational material for Healthcare Professionals should contain the following key elements:

1. XALKORI prolongs the QTc interval which may lead to an increased risk for ventricular tachyarrhythmias (e.g. Torsade de Pointes) or sudden death.
2. 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).
3. XALKORI should be administered with caution to patients:
    a. Who have a history of or predisposition for QTc prolongation.
    b. Who are taking medicinal products that are known to prolong the QT interval.
4. The need for a periodic monitoring with electrocardiograms and electrolytes should be considered when using XALKORI in these patients.
5. Patients who develop a grade 3 QTc prolongation should stop taking XALKORI until recovery to Grade ≤1, then resume at 200 mg twice daily.
6. Patients who develop a grade 4 QTc prolongation should stop taking XALKORI permanently.
7. That XALKORI may cause vision disorders, including diplopia, photopsia, blurred vision, visual impairment, and vitreous floaters.
8. Ophthalmological evaluation should be considered if vision disorder persists or worsens in severity.
9. The concomitant use of XALKORI with strong CYP3A4 inhibitors/inducers and CYP3A4 substrates with narrow therapeutic indices should be avoided.
10. The need to counsel patients about the risk of prolonged QTc and vision disorders and inform them of what symptoms and signs to be aware of and the actions to take.
11. The role and use of the Patient Alert Card.

- **SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION**

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
The MAH should submit the CSR of study A8081007, expected in Q1 2013. The CSR should also include a detailed analysis of outcome on post-progression treatments in Study 1007 as well as efficacy and baseline data according to race (Caucasian/Asian) by treatment groups.	Q1 2013
The MAH should submit updated safety (SAEs and deaths) and efficacy (PFS, OS) data for both studies 1001 and 1005. The MAH should compare and explain potential differences in OS for crizotinib in the 3 studies (1001, 1005 and 1007).	Q1 2013
The MAH should submit the safety review of main (severe) hepatic disorders from all available main studies of crizotinib (including 1001, 1005 and 1007).	Q1 2013

- **OBLIGATION TO CONDUCT POST-AUTHORISATION MEASURES**

The MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to address the question of comparative benefit/risk (crizotinib vs. chemotherapy) in patients with non adenocarcinoma histology ALK positive NSCLC, the MAH must provide additional data/analyses, including comparative data from the comparative study (A8081007) in order to address the benefit/risk of crizotinib (PFS/OS/ORR/safety) versus chemotherapy in ALK positive NSCLC patients according to histology (adenocarcinoma versus other).	Q1 2013

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

XALKORI 200 mg hard capsules
Crizotinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 200 mg crizotinib

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

XALKORI 200 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR BLISTER

1. NAME OF THE MEDICINAL PRODUCT

XALKORI 200 mg hard capsules
Crizotinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 200 mg crizotinib

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

XALKORI 200 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

XALKORI 200 mg hard capsules
Crizotinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Ltd (as MA holder logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

XALKORI 250 mg hard capsules
Crizotinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 250 mg crizotinib

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

XALKORI 250 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR BLISTER

1. NAME OF THE MEDICINAL PRODUCT

XALKORI 250 mg hard capsules
Crizotinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 250 mg crizotinib

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

XALKORI 250 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

XALKORI 250 mg hard capsules
Crizotinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Ltd (as MA holder logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

XALKORI 200 mg hard capsules
XALKORI 250 mg hard capsules
Crizotinib

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What XALKORI is and what it is used for

XALKORI is an anticancer medicine containing the active substance crizotinib used to treat adults with a type of lung cancer called non-small cell lung cancer, that presents with a specific rearrangement or defect in a gene called anaplastic lymphoma kinase (ALK).

XALKORI can be prescribed to you if your disease is at an advanced stage and previous treatment has not helped to stop your disease.

XALKORI may slow or stop the growth of lung cancer. It may help shrink tumours.

If you have any questions about how XALKORI works or why this medicine has been prescribed for you, ask your doctor.

2. What you need to know before you take XALKORI

Do not take XALKORI
- If you are allergic to crizotinib or any of the other ingredients of this medicine (listed in Section 6, "What XALKORI contains"), do not take this medicine.
- If you have a severe liver disease.

Warnings and precautions
Talk to your doctor before taking XALKORI:

- If you have ever had mild or moderate liver disease.

If you have ever had any other lung problems. Some lung problems may get worse during treatment with XALKORI, as XALKORI may cause inflammation of the lungs during treatment. Symptoms may be similar to those from lung cancer. Tell your doctor right away if you have any new or worsening symptoms including difficulty in breathing or shortness of breath, cough with or without mucous or fever.

- If you have been told that you have an abnormality of your heart tracing after an electrocardiogram (ECG) known as prolonged QT interval.

- If you have vision disorders (seeing flashes of light, blurred vision, and double vision).

- If you are currently treated with any of the medicines listed in section ***Other medicines and XALKORI.***

Most of the available information is available in patients with some specific histology type of ALK-positive NSCLC (adenocarcinoma) and limited information is available in the other histologies.

Children and adolescents

Treatment of children and adolescents with this medicine is not recommended. The indication does not cover children and adolescents.

Other medicines and XALKORI
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including herbal medicines and medicine obtained over the counter.

In particular, the following medicines may increase the risk of side effects with XALKORI:
- Clarithromycin, telithromycin, troleandomycin, antibiotics used to treat bacterial infections.
- Ketoconazole, itraconazole, voriconazole, used to treat fungal infections.
- Atazanavir, indinavir, nelfinavir, ritonavir, saquinavir, used to treat HIV infections/AIDS.

The following medicines may reduce the effectiveness of XALKORI:
- Phenytoin, carbamazepine or phenobarbital, anti-epileptics used to treat seizures or fits.
- Rifabutin, rifampicin, used to treat tuberculosis.
- St. John's Wort (*Hypericum perforatum*), a herbal product used to treat depression.

XALKORI may increase side effects associated with the following medicines:
- Alfentanil, and other short acting opiates such as fentanyl (painkillers used for surgical procedures).
- Quinidine, digoxin, disopyramide, amiodarone, sotalol, dofetilide, ibutilide, verapamil, diltiazem used to treat heart problems.
- Pimozide, used to treat mental illness.
- Cisapride, used to treat stomach problems.
- Ciclosporin, sirolimus and tacrolimus used in transplant patients.
- Ergot alkaloids (e.g., ergotamine, dihydroergotamine), used to treat migraine.
- Dabigatran, anticoagulant used to slow down clotting of the blood.
- Colchicine, used to treat gout.
- Pravastatin, used to reduce cholesterol levels.
- Clonidine, guanfacine, used to treat hypertension.
- Mefloquine, used for the prevention of malaria.
- Pilocarpine, used to treat glaucoma (a severe eye disease).
- Anticholinesterases, used to restore muscle function.
- Antipsychotics, used to treat mental illness.
- Moxifloxacine, used to treat bacterial infections.
- Methadone, used to treat pain and for the treatment of opioid dependence.

These medicines *should be avoided* during your treatment with XALKORI.

Oral contraceptives
If you take XALKORI whilst using oral contraceptives, the oral contraceptives may be ineffective.

XALKORI with food and drink
You can take XALKORI with or without food; however, you should avoid drinking grapefruit juice or eating grapefruit while on treatment with XALKORI as they may change the amount of XALKORI in your body.

Pregnancy and breast-feeding
Talk to your doctor or pharmacist before taking this medicine if you are pregnant, may become pregnant or are breast-feeding.

It is recommended that women avoid becoming pregnant and that men do not father children during treatment with XALKORI because XALKORI could harm the baby. If there is any possibility that the person taking this medicine may become pregnant or father a child, they must use adequate contraception during treatment, and for at least 90 days after completing therapy as oral contraceptives may be ineffective while taking XALKORI.

Do not breast-feed during treatment with XALKORI. XALKORI could harm a breast-fed baby.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
You should take special care when driving and using machines as patients taking XALKORI may experience visual disturbances, dizziness, and tiredness.

3. How to take XALKORI

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

- The recommended dose is one capsule of 250 mg taken orally twice daily (total amount 500 mg).
- Take the capsule once in the morning and once in the evening.
- Take the capsules at about the same time each day.
- You can take the capsules with or without food always avoiding grapefruit.
- Swallow the capsules whole and do not crush, dissolve or open the capsules.

If necessary, your doctor may decide to reduce the dose to 200 mg to be taken orally twice daily (total amount 400 mg) and if further dose reduction is necessary, to reduce it to 250 mg to be taken orally once daily.

If you take more XALKORI than you should
If you accidentally take too many capsules, tell your doctor or pharmacist right away. You may require medical attention.

If you forget to take XALKORI
What to do if you forget to take a capsule depends on how long it is until your next dose.
• If your next dose is in **6 hours or more**, take the missed capsule as soon as you remember.
Then take the next capsule at the usual time.
• If your next dose is in **less than 6 hours**, skip the missed capsule.
Then take the next capsule at the usual time.
Tell your doctor about the missed dose at your next visit.

Do not take a double dose (two capsules at the same time) to make up for a forgotten capsule.

If you stop taking XALKORI

It is important to take XALKORI every day, as long as your doctor prescribes it to you. If you are not able to take the medicine as your doctor prescribed, or you feel you do not need it anymore, contact your doctor right away.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you experience any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet.

Some side effects could be serious. You should immediately contact your doctor if you experience any of the following serious side effects (see also section 2 "What you need to know before you take XALKORI "):

- Abnormal liver function
  Tell your doctor right away if you feel more tired than usual, your skin and whites of your eyes turn yellow, your urine turns dark or brown (tea colour), you have nausea, vomiting, or decreased appetite, you have pain on the right side of your stomach, you have itching, or if you bruise more easily than usual. Your doctor may do blood tests to check your liver function, and if the results are abnormal, your doctor may decide to reduce the dose of XALKORI or stop your treatment.

- Lung inflammation
  Tell your doctor right away if you experience difficulty in breathing, especially if associated with cough or fever.

- Light-headedness, fainting, or chest discomfort
  Tell your doctor right away if you experience these symptoms which could be signs of changes in the electrical activity (seen on electrocardiogram) or abnormal rhythm of the heart. Your doctor may perform electrocardiograms to check there are no problems with your heart during treatment with XALKORI.

Other side effects of XALKORI may include:

Very common side effects (may affect more than 1 patient in 10)

- Abnormalities in liver blood tests.
- Visual effects (seeing flashes of light, blurred vision, or double vision, often beginning soon after starting treatment with XALKORI).
- Neuropathy (feeling of numbness or pins and needles in the joints, extremities, or muscles).
- Dizziness.
- Tiredness.
- Oedema (excess fluid in body tissue, causing swelling of the hands and feet).
- Stomach upset, including nausea, vomiting, diarrhoea, constipation, and oesophageal (gullet) disorders.
- Decreased appetite.
- Alteration in sense of taste.
- Skin rash.

*Common side effect*s (may affect 1 to 10 patients in 100)

- Reduction in the number of red blood cells (anemia), white blood cells (which are important in fighting infection) and platelets (which are important for blood clotting).
- Indigestion.
- Reduced heart rate.

Uncommon side effects (may affect up to 1 to 10 patients in 1,000)

- Closed pouches of fluid within the kidneys (complex kidney cysts).

5. How to store XALKORI

- Keep this medicine out of the sight and reach of children
- Do not use this medicine after the expiry date (EXP) which is stated on the bottle or blister foil and carton. The expiry date refers to the last day of that month
- This medicine does not require any special storage conditions
- Do not use any pack that is damaged or shows signs of tampering

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What XALKORI contains

– The active substance in XALKORI is crizotinib. XALKORI capsules come in different strengths.
XALKORI 200 mg: each capsule contains 200 mg crizotinib
XALKORI 250 mg: each capsule contains 250 mg crizotinib

– The other ingredients are:
Capsule content: silica, colloidal anhydrous, cellulose microcrystalline, calcium hydrogen phosphate, anhydrous, sodium starch glycolate (Type A), magnesium stearate.
Capsule shell: gelatin, titanium dioxide (E171), and red iron oxide (E172).
Printing ink: shellac, propylene glycol, potassium hydroxide, and black iron oxide (E172).

What XALKORI looks like and contents of the pack

XALKORI 200 mg is supplied as hard gelatin capsules with pink cap and white body, printed with black ink “Pfizer” on the cap, “CRZ 200” on the body.

XALKORI 250 mg is supplied as hard gelatin capsules with pink cap and body, printed with black ink “Pfizer” on the cap, “CRZ 250” on the body.

It is available in blister packs of 60 hard capsules and in plastic bottles of 60 hard capsules.

Not all pack sizes may be marketed.

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This leaflet was last revised in {MM/YYYY}**.**

This medicine has been given "conditional approval".
This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

ANNEX IV

CONCLUSIONS ON THE GRANTING OF THE CONDITIONAL MARKETING AUTHORISATION AND PRESENTED BY THE EUROPEAN MEDICINES AGENCY

Conclusions presented by the European Medicines Agency on:

- **Conditional marketing authorisation**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the conditional marketing authorisation as further explained in the European Public Assessment Report.