SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Crizotinib 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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Crizotinib 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 Crizotinib 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 Crizotinib (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 Crizotinib 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 Crizotinib 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. Crizotinib 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. Crizotinib must be permanently discontinued in case of further Grade 4 recurrence.

Table 2. Crizotinib 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 d1 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. Crizotinib 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. Crizotinib should be withheld if pneumonitis is suspected, and must be permanently discontinued if treatment-related pneumonitis is diagnosed.

Hepatic impairment

Crizotinib 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 Crizotinib should be used with caution in patients with mild and moderate hepatic impairment (see Table 2 and section 4.8). Crizotinib 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 Crizotinib 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 Crizotinib 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 Crizotinib 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. Crizotinib 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

Crizotinib 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. Crizotinib treatment should be withheld if pneumonitis is suspected. Other causes of pneumonitis should be excluded, and Crizotinib 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). Crizotinib 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 Crizotinib 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 Crizotinib.

Adequate contraceptive methods should be used during therapy, and for at least 90 days after completing therapy (see section 4.5).

Pregnancy

Crizotinib 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 Crizotinib (see section 5.3).

Fertility

Based on nonclinical safety findings, male and female fertility may be compromised by treatment with Crizotinib (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

Crizotinib 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 Crizotinib (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

Data described below reflect exposure to Crizotinib 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 Crizotinib. 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 Crizotinib 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. Crizotinib 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 Crizotinib overdose. Treatment of overdose with the medicinal product consists of general supportive measures. There is no antidote for Crizotinib.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-neoplastic agents, protein kinase inhibitor.

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 Crizotinib 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 Crizotinib 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 Crizotinib 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_{ll} 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 28 hard capsules.

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

Beacon Pharmaceutical Limited

8. MARKETING AUTHORISATION NUMBER(S)

341-293-10

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20-07-2016

10. DATE OF REVISION OF THE TEXT

19-07-2021