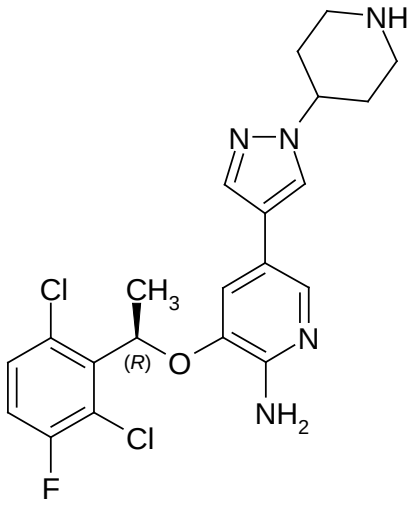
PRODUCT INFORMATION

XALKORI® (crizotinib)

NAME OF THE MEDICINE

Australian Approved Name (AAN): Crizotinib

Chemical Structure:



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

Molecular Formula: $C_{21}H_{22}Cl_2FN_5O$

Molecular Weight: 450.34 Daltons

CAS Registry Number: 877399-52-5

DESCRIPTION

Crizotinib is a white to pale yellow powder with a pKa of 9.4 (piperidinium cation) and 5.6 (pyridinium cation). The solubility of crizotinib in aqueous media decreases over the range pH 1.6 to pH 8.2 from greater than 10 mg/mL to less than 0.1 mg/mL. The log of the distribution coefficient (octanol/water) at pH 7.4 is 1.65.

XALKORI is supplied as hard gelatin capsules containing 200 mg or 250 mg of crizotinib and the following inactive ingredients: microcrystalline cellulose, anhydrous calcium hydrogen phosphate, sodium starch glycollate, magnesium stearate and colloidal anhydrous silica.

The capsules are differentiated by size, colour and printing. The capsule shells for the 200 mg strength consist of a pink opaque cap and white opaque body and the capsule shells for the 250 mg strength consist of a pink opaque cap and body. The pink opaque capsule shell components contain gelatin, titanium dioxide and iron oxide red. The white opaque capsule shell components contain gelatin and titanium dioxide. The capsule shells are printed with black printing ink.

PHARMACOLOGY

Pharmacodynamics

Crizotinib is an inhibitor of the ALK receptor tyrosine kinase (RTK) and its oncogenic variants (i.e., ALK fusion events). 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 growth inhibitory activity and induced apoptosis in tumour cell lines exhibiting ALK fusion events (including EML4-ALK and NPM-ALK). Crizotinib demonstrated antitumour activity in mice bearing tumour xenografts that expressed ALK fusion proteins. The antitumour 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*.

Pharmacokinetics

Absorption

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

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

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%; in the *in vitro* study, there was variability in the fraction of unbound crizotinib at a clinically relevant concentration. *In vitro* studies suggest that crizotinib is a substrate for P-glycoprotein (P-gp). The blood-to-plasma concentration ratio is approximately 1.

Metabolism

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

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

Excretion

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 radiolabelled crizotinib dose to healthy subjects, 63% and 22% of the administered dose was recovered in faeces and urine, respectively. Unchanged crizotinib represented approximately 53% and 2.3% of the administered dose in faeces and urine, respectively.

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

Pharmacokinetics in Special Patient Groups

Hepatic Insufficiency

As crizotinib is extensively metabolised in the liver, hepatic impairment is likely to increase plasma crizotinib concentrations. However, crizotinib has not been studied in patients with hepatic impairment. Clinical studies that were conducted excluded patients with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.5 x ULN or, if due to underlying malignancy, >5.0 x ULN or with total bilirubin >1.5 x ULN.

Renal Insufficiency

Patients with mild (creatinine clearance [CLcr] 60 to <90 mL/min) and moderate (CLcr 30 to <60 mL/min) renal impairment were enrolled in single-arm Studies 1001 and 1005. The effect of renal function, as measured by baseline CLcr on observed crizotinib steady state trough concentrations ($C_{trough, ss}$) was evaluated.

No starting dose adjustment is recommended for patients with mild or moderate renal impairment. An adjustment of the dose of crizotinib is recommended when administering crizotinib to patients with severe renal impairment (CLcr <30 mL/min) not requiring peritoneal dialysis or haemodialysis (see DOSAGE AND ADMINISTRATION – Dose Modification – *Renal Impairment*).

Age

Age has no effect on crizotinib pharmacokinetics.

Body weight and gender

There is no clinically meaningful effect of body weight or gender on crizotinib pharmacokinetics.

Ethnicity

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

Cardiac Electrophysiology

The QT interval prolongation potential of crizotinib was assessed in all patients who received crizotinib 250 mg twice daily. Serial ECGs in triplicate were collected following a single dose and at steady-state to evaluate the effect of crizotinib on QT intervals. Sixteen of 1196 patients (1.3%) were found to have QTcF (corrected QT by the Fridericia method) ≥500 msec and 51 of 1165 patients (4.4%) 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.

CLINICAL TRIALS

Randomised Phase 3 Study 1007

The use of single-agent crizotinib in the treatment of ALK-positive advanced NSCLC with or without brain metastases was investigated in a multicentre, multinational, randomised, open-label Phase 3 study (Study 1007). The primary objective of this study was to demonstrate that crizotinib 250 mg orally twice daily was superior to standard-of-care chemotherapy (pemetrexed 500 mg/m^2 or docetaxel 75 mg/m^2) intravenously (IV) every 21 days in prolonging Progression-Free Survival (PFS) in patients with ALK-positive advanced NSCLC who had received one prior chemotherapy regimen. Patients were required to have ALK-positive NSCLC as identified by FISH prior to randomisation. Patients randomised to chemotherapy could cross over to receive crizotinib in Study 1005 upon Response Evaluation Criteria in Solid Tumors (RECIST)-defined disease progression confirmed by independent radiology review (IRR). The primary efficacy endpoint was PFS with disease progression events determined by IRR. Secondary endpoints included Objective Response Rate (ORR) as determined by IRR, Duration of Response (DR), Overall Survival (OS) and Patient-Reported Outcomes (PRO). The full analysis population for Study 1007 included 347 patients with ALK-positive advanced NSCLC. One hundred seventy-three (173) patients were randomised to the crizotinib arm (172 patients received crizotinib) and 174 patients were randomised to the chemotherapy arm, (99 [58%] patients received pemetrexed and 72 [42%] patients received docetaxel). Randomisation was stratified by ECOG performance status (PS) (0-1, 2), brain metastases (present, absent) and prior EGFR tyrosine kinase inhibitor treatment (yes, no). The median duration of study treatment was 31 weeks in the crizotinib arm as compared to 12 weeks in the chemotherapy arm.

Patients could continue treatment as assigned beyond the time of RECIST-defined disease progression, as assessed by IRR, at the discretion of the investigator if the patient was still experiencing clinical benefit. Fifty eight of 84 (69%) crizotinib-treated patients and 17 of 119 (14%) chemotherapy-treated patients continued treatment for at least 3 weeks after objective disease progression.

Key demographic and baseline characteristics for patients in this study were comparable between the crizotinib and chemotherapy arms as shown in Table 1.

Table 1. Demographic and Disease Characteristics in Randomised Phase 3 Study 1007 (Full Analysis Population)

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

The following information is from a preliminary analysis. At the cut-off point, 343 of the 347 randomised subjects had received study treatment (172 crizotinib; 171 chemotherapy). Of these, 113 were receiving on-going treatment at the data cut-off point (85 crizotinib; 28 chemotherapy).

Crizotinib significantly prolonged PFS compared to chemotherapy as assessed by IRR. The median PFS was 7.7 months for patients randomised to crizotinib and 3.0 months for patients randomised to chemotherapy. The hazard ratio was 0.487 with a p-value of <0.0001 (1-sided, based on stratified log-rank test). The median PFS for patients treated with crizotinib was 7.7 months and 4.2 months for patients treated with pemetrexed. The hazard ratio was 0.589 with a p-value of 0.0004 (1-sided, based on stratified log-rank test). The median PFS for patients treated with crizotinib was 7.7 months and 2.6 months for patients treated with docetaxel. The hazard ratio was 0.298 with a p-value of <0.0001 (1-sided stratified log-rank test).

Crizotinib also significantly improved IRR-assessed ORR as compared to chemotherapy with a p-value of <0.0001 (2-sided stratified test). The ORR for patients randomised to crizotinib was 65% (95% CI: 58%, 72%) and for patients randomised to chemotherapy was 20% (95% CI: 14%, 26%). The ORR for patients treated with crizotinib was 66% (95% CI: 58%, 73%) and 29% (95% CI: 21%, 39%) for patients treated with pemetrexed, with a p-value of <0.0001 (2-sided stratification test). The ORR for patients treated with crizotinib was 66% (95% CI: 58%, 73%) and 7% (95% CI: 2%, 16%) for patients treated with docetaxel, with a p-value of <0.0001 (2-sided stratified test).

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

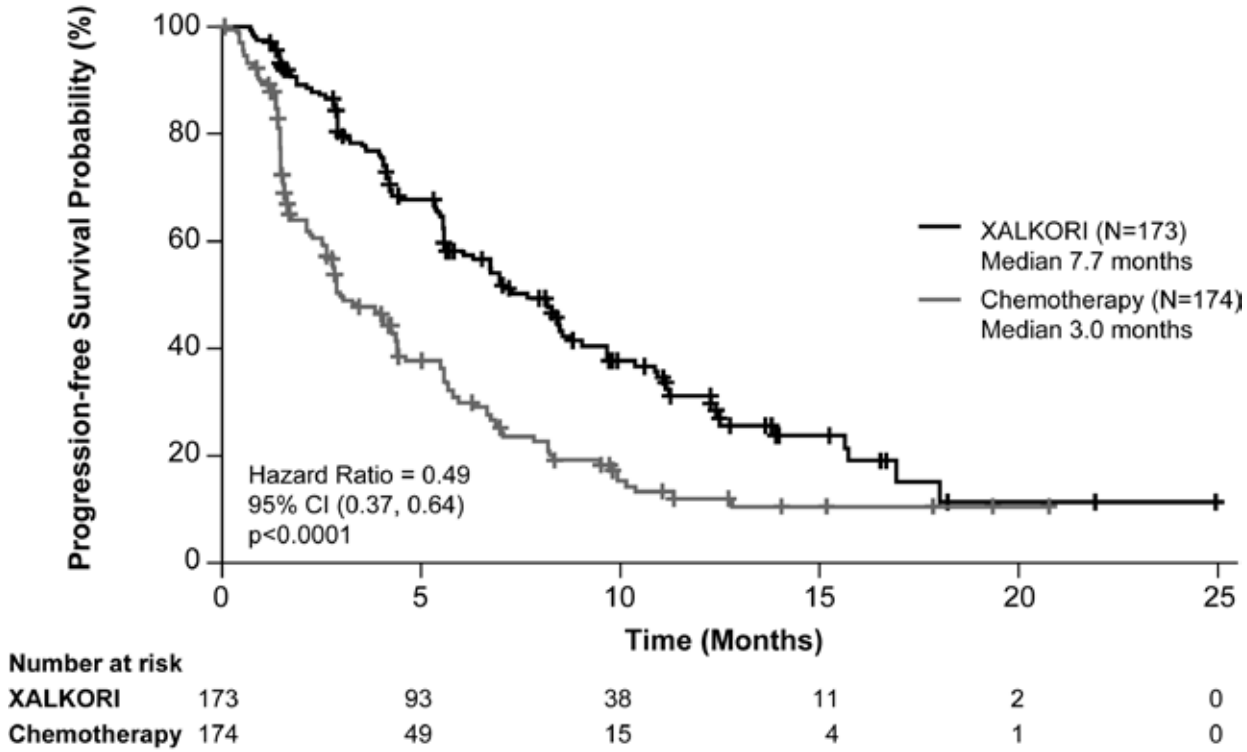
The median OS with crizotinib was 20.3 months and 22.8 months with chemotherapy. OS data were, however, not mature at the time of analysis, as only approximately 40% of the number of protocol-specified events had been reached. The OS analysis was not adjusted for the potentially confounding effects of crossover to subsequent therapy outside of Study 1007. Of the 174 patients in the chemotherapy arm, 112 (64.4%) patients subsequently received crizotinib treatment.

Efficacy data from Study 1007 are summarised in Table 2 and the Kaplan-Meier curve for PFS is shown in Figure 1.

Table 2. ALK-Positive Advanced NSCLC Efficacy Results from Randomised Phase 3 Study 1007 (Full Analysis Population)

Efficacy Parameter	Crizotinib (N=173)	Chemotherapy (N=174)
PFS [median (95% CI)] months	7.7 (6.0, 8.8)	3.0 (2.6, 4.3)
ORR [% (95% CI)]	65 (58, 72)	20 (14, 26)

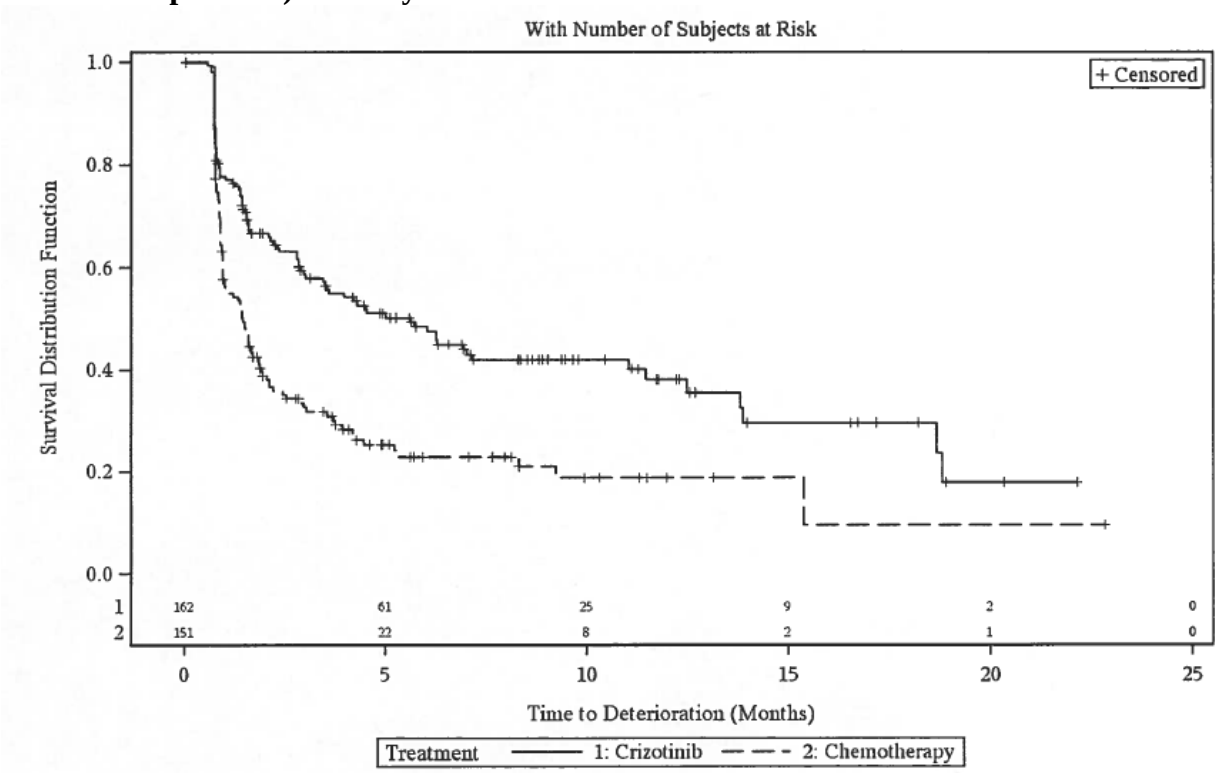
Figure 1. Kaplan-Meier Curves for Progression-Free Survival by Treatment Arm in Randomised Phase 3 Study 1007 (Full Analysis Population)



Time to Deterioration (TTD) was pre-specified as the first occurrence of a ≥10-point increase in scores from baseline in symptoms of pain (EORTC QLQ-LC13 pain in chest), cough (EORTC QLQ-LC13 cough) or dyspnoea (EORTC QLQ-LC13 dyspnoea). The median TTD in patient-reported pain in chest, dyspnoea or cough as a composite endpoint was 5.6 months (95% CI: 3.4 months, 11.0 months) in the crizotinib arm compared to 1.4 months (95% CI: 1.0 months, 1.8 months) in the chemotherapy arm. Treatment with crizotinib was associated with a significantly longer TTD in the symptoms of pain in chest, dyspnoea or cough compared to chemotherapy (hazard ratio 0.535; 95% CI: 0.404, 0.709; Hochberg adjusted log-rank p<0.0001). The Kaplan-Meier Plot of TTD in pain in chest, dyspnoea or cough as a composite endpoint by arm for the patient-reported outcome evaluable population is shown in Figure 2.

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

Figure 2. Kaplan-Meier Plot of Time to Deterioration in Pain (in Chest), Dyspnoea or Cough (Composite Endpoint) by Arm (Patient-Reported Outcome Evaluable Population) in Study 1007.



Single-Arm Studies in ALK-Positive Advanced NSCLC

The use of single-agent crizotinib in the treatment of ALK-positive advanced NSCLC with or without brain metastases was investigated in two multicentre, multinational, single-arm studies (Studies 1001 and 1005). Patients enrolled into these studies had received prior systemic therapy, with the exception of 24 patients in Study 1001 who had no prior systemic treatment for locally advanced or metastatic disease. The primary efficacy endpoint in both studies was ORR according to RECIST. Secondary endpoints included Time to Tumour Response (TTR), DR, Disease Control Rate (DCR), PFS and OS.

Patients received 250 mg of crizotinib orally twice daily. Demographic and disease characteristics for Studies 1001 and 1005 are provided in Table 3.

Table 3. Demographic and Disease Characteristics in Studies 1001 and 1005

Characteristics	Study 1001 N=149	Study 1005 N=261
Sex, n (%)		
Male	73 (49)	119 (46)
Female	76 (51)	142 (54)
Age (years), n (%)		
Median (range)	52 (21-86)	52 (24-82)
<65 years	129 (87)	231 (89)
≥65 years	20 (13)	30 (11)
Race, n (%)		
White	95 (64)	152 (58)
Black	5 (3)	8 (3)
Asian	41 (28)	96 (37)
Other	8 (5)	5 (2)
Smoking Status, n (%)[a]		
Never smoked	106 (71)	176 (67)
Former smoker	42 (28)	73 (28)
Current smoker	1 (1)	12 (5)
Disease Stage, n (%)		
Locally advanced	9 (6)	21 (8)
Metastatic	140 (96)	240 (92)
Histological Classification, n (%)		
Adenocarcinoma	144 (97)	242 (93)
Large cell carcinoma	1 (1)	4 (2)
Squamous cell carcinoma	2 (1)	3 (1)
Adenosquamous carcinoma	0 (0)	3 (1)
Other	2 (1)	9 (3)
ECOG PS at Baseline, n (%)		
0	56 (38)	67 (26)
1	75 (50)	147 (56)
2 – 3[b]	18 (12)	47 (18)
Prior Radiation Therapy		
No	63 (42)	107 (41)
Yes	86 (58)	153 (59)
Not Reported	0 (0)	1 (1)
Prior Systemic Therapy for Advanced Disease Number of Advanced/Metastatic Regimens		
0	24 (16)	0 (0)
1	47 (32)	27 (10)
2	31 (21)	90 (35)
≥3	47 (32)	144 (55)

[a] Smoking status was determined by investigator
[b] Includes 1 patient with an ECOG PS of 1 at screening but was 3 at baseline

In Study 1001, 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 forty-nine patients with ALK-positive advanced NSCLC were enrolled into Study 1001 at the time of data cutoff. The median duration of treatment was 43 weeks. There were 3 complete responses and 85 partial responses for an ORR of 62%. The median response duration was 49.1 weeks. There were an additional 30 patients who had stable disease for a DCR at 8 weeks of 83%. Fifty-one percent of objective tumour responses were achieved during the first 8 weeks of treatment.

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

Two hundred sixty-one patients with ALK-positive advanced NSCLC from Study 1005 were analysed at the time of data cutoff. The median duration of treatment was 25 weeks. There were 4 complete responses and 132 partial responses for an ORR of 53%. The median response duration was 42.9 weeks. There were an additional 80 patients who had stable disease for a DCR at 6 weeks of 85%. Seventy-seven percent of objective tumour responses were achieved during the first 8 weeks of treatment.

Efficacy data from Studies 1001 and 1005 are provided in Table 4.

Table 4: ALK-Positive Advanced NSCLC Efficacy Results from Studies 1001 and 1005

Efficacy Parameter	**Study 1001 (N=149)**	**Study 1005 (N=261)**
ORR[a] [% (95% CI)]	62 (53, 70)	53 (47, 60)
TTR [median (range)] weeks	7.9 (2.1, 57.3)	6.1 (4.9, 30.4)
DR[b] [median (95% CI)] weeks	49.1 (39.3, 89.3)	42.9 (36.1, 49.7)
DCR[a, c] at 8 weeks (Study 1001) [% (95% CI)]; at 6 weeks (Study 1005) [% (95% CI)]	83% (75%, 88%)	85% (80%, 89%)
PFS[b] [median (95% CI)] months	9.9 (7.7, 13.4)	8.5 (6.5, 9.9)
OS probability at 12 months[b] [% (95% CI)]	75 (66, 82)	61 (49, 71)

[a] 6 patients were not evaluable for response in Study 1001 and 6 patients were not evaluable for response in Study 1005

[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 1001) or at 6 weeks (Study 1005).

INDICATIONS

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

CONTRAINDICATIONS

Use of XALKORI is contraindicated in patients with hypersensitivity to crizotinib or to any of the excipients.

PRECAUTIONS

The data described below relate to exposure to crizotinib in 172 patients with ALK-positive advanced NSCLC who participated in randomised Phase 3 Study 1007 and in 1083 patients with ALK-positive NSCLC who participated in two single-arm clinical trials (Studies 1001 and 1005).

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×ULN and total bilirubin greater than 2×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 17% of patients in Study 1007, 7% of patients in Study 1001 and 8% of patients in Study 1005. Grade 3 and 4 elevations were generally asymptomatic and reversible upon dosing interruption. Patients usually resumed treatment at a lower dose without recurrence; however, 2 patients from Study 1007 (1%), 1 patient from Study 1001 (<1%) and 6 patients from Study 1005 (<1%) required permanent discontinuation from treatment. Transaminase elevations generally occurred within the first 2 months of treatment. Liver function tests including ALT and total bilirubin should be monitored every 2 weeks during the first 2 months of treatment, then once a month and as clinically indicated, with more frequent repeat testing for Grades 2, 3 or 4 elevations. For patients who develop transaminase elevations, see DOSAGE AND ADMINISTRATION - Dose Modification.

Interstitial Lung Disease (Pneumonitis)

XALKORI has been associated with severe, life-threatening or fatal interstitial lung disease (ILD)/pneumonitis in clinical trials with a frequency of 19 in 1255 (1.5%) patients across Studies 1007, 1001 and 1005. These cases generally occurred within 2 months after the initiation of treatment. Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis. Other potential causes of pneumonitis should be excluded. XALKORI should be permanently discontinued in patients diagnosed with treatment-related ILD/pneumonitis (see DOSAGE AND ADMINISTRATION - Dose Modification).

QT Interval Prolongation

Automated machine-read QTc prolongation without accompanying arrhythmia has been observed (see PHARMACOLOGY - *Cardiac Electrophysiology*). XALKORI should be administered with caution to patients who have a history of or predisposition for QTc prolongation, or who are taking medications 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 DOSAGE AND ADMINISTRATION - Dose Modification.

Bradycardia

Bradycardia has been reported in clinical studies and it was usually asymptomatic. The full effect of crizotinib on pulse rate may not develop until several weeks after start of treatment. Avoid using crizotinib in combination with other bradycardic agents (e.g., beta-blockers, non-dihydropyridine calcium channel blockers such as verapamil and diltiazem, clonidine, digoxin) to the extent possible, due to the increased risk of symptomatic bradycardia (syncope, dizziness, hypotension). Monthly monitoring of pulse rate and blood pressure is recommended. Dose modification is not required in cases of asymptomatic bradycardia. In cases of symptomatic bradycardia, crizotinib should be withheld and the use of concomitant medications should be re-evaluated. For management of patients who develop symptomatic bradycardia, see DOSAGE AND ADMINISTRATION - Dose Modification and ADVERSE EFFECTS).

Leucopenia

Crizotinib has been associated with neutropenia and, less commonly, febrile neutropenia. About 9% of patients treated with crizotinib had Grade 3-4 neutropenia, at which point dosing interruption is recommended (see DOSAGE AND ADMINISTRATION - Dose Modification). Onset of neutropenia may occur after many months of exposure to crizotinib. Lymphopenia has also been observed. Monitor white blood cell count (including differential count) monthly and additionally as clinically indicated (e.g., if Grade 3-4 abnormalities are observed, or if fever or infection occurs).

Effects on Fertility

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 3-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. Exposure at the no effect level was approximately equivalent to the clinical AUC in males and 4 times the clinical AUC in females.

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

Use in Pregnancy Pregnancy Category D

XALKORI may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women using XALKORI. Crizotinib was not shown to be teratogenic in pregnant rats or rabbits, but the maximum doses (200 and 60 mg/kg/day, respectively) were low, resulting in maximum exposures of only 5 and 3 times the clinical exposure based on AUC in rats and rabbits, respectively. Reduced fetal body weights were observed in both species at 200 and 60 mg/kg/day in the rat and rabbit, respectively and were considered adverse effects. Exposure at the no effect level was similar to or below the human clinical exposure based on AUC.

Women of childbearing potential should be advised to avoid becoming pregnant while receiving XALKORI. Women of childbearing potential who are receiving this drug, or partners of women of childbearing potential receiving this drug, should use adequate contraceptive methods during therapy and for at least 90 days after completing therapy.

Female patients taking crizotinib during pregnancy or who become pregnant while taking crizotinib should be apprised of the potential hazard to a fetus. Male patients taking crizotinib should also be apprised of the potential hazard to a fetus if their partner is or should become pregnant.

Use in Lactation

It is not known whether crizotinib and its metabolites are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from exposure to crizotinib, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Paediatric Use

The safety and efficacy of XALKORI in paediatric patients have not been established.

Decreased bone formation in growing long bones was observed in immature rats at 150 mg/kg/day following once daily dosing for 28 days (approximately 10 times human clinical exposure based on AUC in adult patients). Exposure at the no effect level was approximately 3 times the AUC in adult patients at the recommended human dose. Other toxicities of potential concern to paediatric patients have not been evaluated in juvenile animals.

Use in the Elderly

Of the 172 crizotinib-treated patients in Study 1007, 27 (16%) were 65 years or older. Of the 149 patients in Study 1001, 20 (13%) were 65 years or older. Of the 934 patients in Study 1005, 152 (16%) were 65 years or older. No overall differences in safety or efficacy were observed in comparison with younger patients.

Use in Hepatic Impairment

XALKORI should be used with caution in patients with hepatic impairment (see PHARMACOLOGY - Pharmacokinetics in Special Patient Groups – *Hepatic Insufficiency* and Table 7 in DOSAGE AND ADMINISTRATION).

Use in Renal Impairment

If patients have severe renal impairment not requiring peritoneal dialysis or haemodialysis, the dose of crizotinib should be adjusted (see DOSAGE AND ADMINISTRATION – Dose Modification).

Genotoxicity

Crizotinib was genotoxic in an *in vitro* micronucleus assay in Chinese Hamster Ovary cells, in an *in vitro* human lymphocyte chromosome aberration assay and in an *in vivo* rat bone marrow micronucleus assay. Crizotinib was not mutagenic *in vitro* in the bacterial reverse mutation (Ames) assay.

Carcinogenicity

Carcinogenicity studies with crizotinib have not been performed.

Effects on Ability to Drive and Use of Machines

No studies on the effect of crizotinib on the ability to drive and use machines have been performed. However, caution should be exercised when driving or operating machinery by patients who experience vision disorder, dizziness or fatigue while taking XALKORI.

INTERACTIONS WITH OTHER MEDICINES

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

Agents that may increase crizotinib plasma concentrations

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

Therefore, the concomitant use of strong CYP3A inhibitors (certain protease inhibitors such as atazanavir, indinavir, ritonavir and saquinavir, certain azole antifungals such as itraconazole, ketoconazole and voriconazole, certain macrolides such as clarithromycin and troleandomycin) should be avoided. Grapefruit or grapefruit juice may also increase plasma concentrations of crizotinib and should be avoided. However, the effect of CYP3A inhibitors on steady-state crizotinib exposure has not been established.

Crizotinib is a substrate for P-glycoprotein. The effect of P-glycoprotein inhibitors on the disposition of crizotinib has not been assessed *in vivo*.

Agents that may decrease crizotinib plasma concentrations

Coadministration of a single 250 mg crizotinib dose with rifampicin (600 mg once daily), 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. However, the effect of CYP3A inducers on steady-state crizotinib exposure has not been established.

Agents whose plasma concentrations may be altered by crizotinib

Crizotinib has been identified as an inhibitor of CYP3A both *in vitro* and *in vivo*. Caution should be exercised in administering crizotinib in combination with drugs that are predominantly metabolised by CYP3A, particularly those CYP3A substrates that have narrow therapeutic indices, including but not limited to alfentanil, ciclosporin, fentanyl, quinidine, sirolimus and tacrolimus.

Coadministration of crizotinib should be avoided with CYP3A substrates that have narrow therapeutic indices and are associated with life-threatening arrhythmias, including but not limited to dihydroergotamine, ergotamine and pimozide.

Coadministration of Crizotinib and CYP3A Substrates

Following 28 days of crizotinib dosing at 250 mg taken twice daily in cancer patients, the oral midazolam AUC was 3.7-fold (90% CI: 2.63-5.07) those seen when midazolam was administered alone, suggesting that crizotinib is a moderate inhibitor of CYP3A.

Coadministration with other CYP Substrates

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

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

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

Coadministration with Drugs that are Substrates of Transporters

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

In vitro, crizotinib did not inhibit the human hepatic uptake transport proteins OATP1B1 or OATP1B3 at clinically relevant concentrations. Therefore, clinical drug-drug interactions are unlikely to occur as a result of crizotinib-mediated inhibition of the hepatic uptake of drugs that are substrates for these transporters.

Coadministration of Crizotinib with Agents that Increase Gastric pH

The aqueous solubility of crizotinib is pH dependent, with low (acidic) pH resulting in higher solubility. In general, drugs that elevate the gastric pH (such as proton pump inhibitors, H2 blockers, or antacids) may decrease the solubility of crizotinib and subsequently reduce its bioavailability. The use of antacids was permitted during crizotinib treatment in patient trials. Based on population pharmacokinetic modelling, coadministration of antacids is unlikely to result in changes in steady-state crizotinib exposure. However, no formal studies have been conducted.

ADVERSE EFFECTS

Summary of Safety Profile

The data described below reflect exposure to crizotinib in 172 patients with ALK-positive advanced NSCLC who participated in randomised Phase 3 Study 1007 and in 1083 patients with ALK-positive NSCLC who participated in two single-arm clinical trials (Studies 1001 and 1005). These patients received a starting oral dose of 250 mg taken twice daily continuously. In Study 1007, the median duration of treatment was 31 weeks for patients on crizotinib. In Study 1001, the median duration of treatment was 32 weeks. In Study 1005, the median duration of treatment was 23 weeks.

Clinical Trials Experience

The most serious adverse reactions in patients with ALK-positive advanced NSCLC are hepatotoxicity, ILD/pneumonitis and QT interval prolongation (see PRECAUTIONS). The most common adverse reactions (≥25%) in patients with ALK-positive NSCLC are vision disorder, nausea, diarrhoea, vomiting, constipation, oedema, elevated transaminases and fatigue.

Randomised Phase 3 Study 1007

The safety analysis population in Study 1007 included 172 patients who received crizotinib and 171 patients who received chemotherapy (99 pemetrexed, 72 docetaxel). The median duration of study treatment was 31 weeks for patients on crizotinib and 12 weeks for patients on chemotherapy.

Dosing interruptions due to treatment-related adverse events occurred in 54 (31%) patients on crizotinib and 14 (8%) patients on chemotherapy. Dose reductions due to treatment-related adverse events occurred in 26 (15%) patients on crizotinib and 24 (14%) patients on chemotherapy. Treatment-related adverse events resulting in permanent discontinuation occurred in 11 (6%) patients on crizotinib and 17 (10%) patients on chemotherapy.

Table 5 compares adverse reactions experienced by patients in both the crizotinib and chemotherapy arms of Study 1007.

Table 5. Adverse Reactions Reported in Patients Who Received Crizotinib or Chemotherapy in Randomised Phase 3 Study 1007

Adverse Reaction	Crizotinib (N=172)		Chemotherapy (N=171)	
	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Blood and Lymphatic System Disorders				
Neutropenia[a]	47 (27)	23 (13)	39 (23)	33 (19)
Leucopenia	15 (9)	3 (2)	9 (5)	4 (2)
Cardiac Disorders				
Electrocardiogram QT prolonged	8 (5)	6 (3)	0 (0)	0 (0)
Bradycardia[b]	8 (5)	0 (0)	0 (0)	0 (0)
Eye Disorders				
Vision Disorder[c]	103 (60)	0 (0)	16 (9)	0 (0)

Gastrointestinal Disorders				
Vomiting	80 (47)	2 (1)	30 (18)	0 (0)
Nausea	94 (55)	1 (1)	64 (37)	1(1)
Diarrhoea	103 (60)	0 (0)	33 (19)	1 (1)
Constipation	73 (42)	4 (2)	39 (23)	0 (0)
Dyspepsia	14 (8)	0 (0)	6 (3)	0 (0)
General Disorders and Administration Site Conditions				
Fatigue	46 (27)	4 (2)	57 (33)	7 (4)
Oedema[d]	54 (31)	0 (0)	27 (16)	0 (0)
Hepatobiliary Disorders				
Elevated Transaminases[e]	66 (38)	27 (16)	25 (15)	4 (2)
Blood alkaline phosphatase increased	13 (8)	1 (1)	6 (4)	0 (0)
Hepatic failure	1 (1)	1 (1)	0 (0)	0 (0)
Metabolism and Nutritional Disorders				
Decreased appetite	47 (27)	4 (2)	45 (26)	3 (2)
Nervous System Disorder				
Neuropathy[f]	33 (19)	1 (1)	29 (17)	2 (1)
Dizziness[g]	37 (22)	1 (1)	14 (8)	0 (0)
Dysgeusia	44 (26)	0 (0)	16 (9)	0 (0)
Renal and Urinary Disorders				
Renal Cyst[h]	7 (4)	0 (0)	1 (1)	0 (0)
Respiratory, Thoracic and Mediastinal Disorders				
Interstitial Lung Disease[i]	7 (4)	1 (1)	1 (1)	0 (0)
Skin and Subcutaneous Tissue Disorders				
Rash	15 (9)	0 (0)	29 (17)	0 (0)

Includes cases reported within the clustered terms:

[a] Neutropenia (Febrile neutropenia, Neutropenia, Neutrophil count decreased)

[b] Bradycardia (Bradycardia, Sinus bradycardia)

[c] Vision Disorder (Diplopia, Photophobia, Photopsia, Vision blurred, Visual acuity reduced, Visual impairment, Vitreous floaters)

[d] Oedema (Face oedema, Generalised oedema, Local swelling, Localised oedema, oedema, oedema peripheral, Periorbital oedema)

[e] Elevated Transaminases (Alanine aminotransferase increased, Aspartate aminotransferase increased, Gamma-glutamyltransferase increased, Hepatic function abnormal, Transaminases increased)

[f] Neuropathy (Dysaesthesia, Gait disturbance, Hypoaesthesia, Muscular weakness, Neuralgia, Neuropathy peripheral, Paraesthesia, Peripheral sensory neuropathy, Polyneuropathy, Skin burning sensation)

[g] Dizziness (Balance disorder, Dizziness, Dizziness postural)

[h] Renal Cyst (Renal cyst)

[i] Interstitial Lung Disease (Acute respiratory distress syndrome, Interstitial lung disease, Pneumonitis)

Single-Arm Studies in ALK-Positive Advanced NSCLC

The safety analysis population in Study 1005 included 934 patients who received crizotinib. The median duration of treatment was 23 weeks. Dosing interruptions and reductions due to treatment-related adverse events occurred in 212 (23%) patients and 116 (12%) patients in Study 1005, respectively. Treatment-related adverse events resulting in permanent discontinuation occurred in 45 (5%) patients in Study 1005. The most common treatment-related adverse events (≥25%) in Study 1005 included vision disorder, nausea, vomiting, diarrhoea, oedema and constipation. The most common Grade 3 or 4 treatment-related adverse events (≥3%) in Study 1005 were neutropenia and elevated transaminases.

The safety analysis population in Study 1001 included 149 patients who received crizotinib. The median duration of treatment was 32 weeks. Dosing interruptions and reductions due to treatment-related adverse events occurred in 22 (15%) patients and 10 (7%) patients in Study 1001, respectively. Treatment-related adverse events resulting in permanent discontinuation occurred in 3 (2%) patients in Study 1001. The most common treatment-related adverse events (≥25%) in Study 1001 were consistent with those in randomised Phase 3 Study 1007 and single-arm Study 1005 and included nausea, vision disorder, diarrhoea, vomiting, constipation and oedema.

Description of Selected Adverse Effects

Visual Effects

Treatment-emergent all-causality vision disorder, most commonly visual impairment, photopsia, blurred vision and vitreous floaters, was experienced by 103 (60%) patients in Study 1007 and 99 (66%) and 513 (55%) patients in Studies 1001 and 1005, respectively. Investigator-assessed treatment-related vision disorder was reported for 101 (59%) patients in Study 1007 and 97 (65%) and 496 (53%) patients in Studies 1001 and 1005, respectively. Greater than 96% of these patients had events that were mild in severity with median times to onset of 5 days, 15 days and 7 days in Studies 1007, 1001 and 1005, respectively. Ophthalmological evaluation should be considered if vision disorder persists or worsens in severity. No patients from Study 1007, 1 patient from Study 1001, and 4 patients from Study 1005 had temporary treatment discontinuation. One patient from Study 1007 and 1 patient from Study 1005 had dose reduction for vision disorder. Permanent discontinuation from crizotinib treatment due to vision disorder was not required for any patients in Studies 1007, 1001 and 1005.

Gastrointestinal Effects

Nausea, diarrhoea, vomiting and constipation were the most commonly reported gastrointestinal events. Median times to onset for nausea and vomiting was 2 to 3 days. Most events were mild to moderate in severity and declined in frequency after 3 to 4 weeks of treatment. Supportive care should include the use of antiemetic medications. In clinical trials, the most commonly used antiemetic medications were ondansetron and prochlorperazine. Diarrhoea and constipation were primarily mild to moderate in severity. Supportive care for diarrhoea and constipation should include the use of standard antidiarrhoeal and laxative medications, respectively.

Nervous System Effects

Treatment-emergent all-causality neuropathy as defined in Table 5 was experienced by 33 (19%) patients in Study 1007 and 36 (24%) and 178 (19%) patients in Studies 1001 and 1005, respectively. Investigator-assessed treatment-related neuropathy was experienced by 14 (8%) of patients in Study 1007 and 15 (10%) and 95 (10%) patients in Studies 1001 and 1005, respectively, and was primarily Grade 1 in severity. Dizziness and dysgeusia were also very commonly reported in these studies and were primarily Grade 1 in severity.

Bradycardia

Treatment-emergent all-causality bradycardia was experienced by 8 (5%) patients in Study 1007 and 13 (9%) and 57 (6%) patients in Studies 1001 and 1005, respectively. Investigator-assessed treatment-related bradycardia was experienced by 7 (4%) patients in Study 1007 and 10 (7%) and 49 (5%) patients in Studies 1001 and 1005, respectively. The majority of these cases were Grade 1 or 2 in severity. In Studies 1007, 1001 and 1005, 19 of 170 (11%) patients, 26 of 144 (18%) patients and 90 of 890 (10%) patients had a pulse rate <50 bpm. The use of concomitant medications associated with bradycardia should be carefully evaluated. Patients who develop symptomatic bradycardia should be managed as recommended in the PRECAUTIONS and DOSAGE AND ADMINISTRATION - Dose Modification sections.

Renal Cyst

Treatment-emergent all-causality complex renal cysts were experienced by 7 (4%) patients in Study 1007 and 1 (<1%) and 12 (1%) patients in Studies 1001 and 1005, respectively. Investigator-assessed treatment-related complex renal cysts were reported in 7 (4%) patients in Study 1007 and 1 (<1%) and 11 (1%) patients in Studies 1001 and Study 1005, respectively. There were no reports of clinically relevant abnormal urinalyses or renal impairment in these cases, although local cystic invasion beyond the kidney was observed in some patients. Periodic monitoring with imaging and urinalysis should be considered in patients who develop renal cysts.

Laboratory Abnormalities/Testing

Haematological Laboratory Abnormalities

In Study 1007, shifts to Grade 3 or 4 decreases in leucocytes and neutrophils were observed at frequencies of 5% and 13%, respectively. In Study 1001, shifts to Grade 3 or 4 decreases in leucocytes and neutrophils were observed in patients at frequencies of <3% and 8% respectively. In Study 1005, shifts to Grade 3 or 4 decreases in leucocytes and neutrophils were observed in patients at frequencies of <3% and 8%, respectively. Complete blood counts including differential white blood cell counts should be monitored as clinically indicated, with more frequent repeat testing if Grade 3 or 4 abnormalities are observed, or if fever or infection occurs. In patients who develop haematologic laboratory abnormalities, see DOSAGE AND ADMINISTRATION - Dose Modification.

Hepatic Laboratory Abnormalities

In Study 1007, increases to Grade 3 or 4 ALT, AST and alkaline phosphatase were observed in patients at frequencies of 17%, 9% and 2%, respectively. In Study 1001, increases to Grade 3 or 4 ALT, AST and alkaline phosphatase were observed in patients at frequencies of 7%, 4% and 0%, respectively. In Study 1005, increases to Grade 3 or 4 ALT, AST and alkaline phosphatase were observed in patients at frequencies of 8%, 4% and 2%, respectively. Patients should be monitored for hepatotoxicity and managed as recommended in the Precautions section (see PRECAUTIONS).

DOSAGE AND ADMINISTRATION

ALK Testing

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

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

Recommended Dosing

The recommended dose schedule of XALKORI is 250 mg taken orally twice daily. Continue treatment as long as the patient is deriving clinical benefit from therapy.

XALKORI may be taken with or without food (see Pharmacokinetics). Capsules should be swallowed whole.

Missed Dose

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

Dose Modification

Dosing interruption and/or dose reduction may be required based on individual safety and tolerability. If dose reduction is necessary, then the dose of XALKORI should be reduced to 200 mg taken orally twice daily and, if further dose reduction is necessary, then reduce the dosage to 250 mg taken orally once daily. Dose reduction guidelines for haematologic and non-haematologic toxicities are provided in Tables 6 and 7.

Table 6. Crizotinib Dose Modification – Haematologic Toxicities[a]

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

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

Table 7. Crizotinib Dose Modification – Non-Haematologic Toxicities

CTCAE[a] Grade	XALKORI Dosing
Grade 3 or 4 ALT or AST elevation with Grade ≤1 total bilirubin	Withhold until recovery to Grade £1 or baseline, then resume at 200 mg twice daily[b]
Grade 2, 3 or 4 ALT or AST elevation with concurrent Grade 2, 3 or 4 total bilirubin elevation (in the absence of cholestasis or haemolysis)	Permanently discontinue
Any Grade interstitial lung disease/ 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
Grade 2, 3 Bradycardia[d] (symptomatic, may be severe and medically significant, medical intervention indicated)	Withhold until recovery to Grade ≤ 1 or to heart rate of 60 bpm or above Evaluate concomitant medications known to cause bradycardia, as well as anti-hypertensive medications If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at previous dose upon recovery to Grade ≤ 1 or to heart rate of 60 bpm or above If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, resume at reduced dose upon recovery to Grade ≤ 1 or to heart rate of 60 bpm or above
Grade 4 Bradycardia[d,e] (life-threatening consequences, urgent intervention indicated)	Permanently discontinue if no contributing concomitant medication is identified If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at 250 mg once daily upon recovery to Grade ≤ 1 or to heart rate of 60 bpm or above, with frequent monitoring.

[a] NCI Common Terminology Criteria for Adverse Events

b In case of recurrence, withhold until recovery to Grade £1, then resume at 250 mg once daily. Permanently discontinue in case of further Grade ≥3 recurrence.

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

d Heart rate less than 60 beats per minute (bpm).

e Permanently discontinue for recurrence.

Hepatic impairment

As crizotinib is extensively metabolised in the liver, hepatic impairment is likely to increase plasma crizotinib concentrations. XALKORI should be used with caution in patients with hepatic impairment (see PHARMACOLOGY - Pharmacokinetics in Special Patient Groups – *Hepatic Insufficiency* and PRECAUTIONS - Hepatotoxicity). For patients who develop transaminase elevations, see Table 7 Crizotinib Dose Modification – Non-Haematologic Toxicities.

Renal impairment

No starting dose adjustment is needed for patients with mild (CLcr 60 to < 90 mL/min) or moderate (CLcr 30 to < 60 mL/min) renal impairment. The crizotinib dose should be adjusted to 250 mg taken orally once daily in patients with severe renal impairment not requiring peritoneal dialysis or haemodialysis. The dose may be increased to 200 mg twice daily based on individual safety and tolerability after at least 4 weeks of treatment (see PHARMACOLOGY - Pharmacokinetics in Special Patient Groups – *Renal Insufficiency*).

OVERDOSAGE

There have been no known cases of XALKORI overdose. Treatment of overdose with XALKORI should consist of general supportive measures. There is no antidote for XALKORI.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26.

PRESENTATION AND STORAGE CONDITIONS

200 mg strength: hard gelatin capsule with white opaque body and pink opaque cap containing a white to pale yellow powder, printed with black ink "Pfizer" on the cap, "CRZ 200" on the body. Bottles or blister packs contain 60 capsules.

250 mg strength: hard gelatin capsule with pink opaque cap and body containing a white to pale yellow powder, printed with black ink "Pfizer" on the cap, "CRZ 250" on the body. Bottles or blister packs contain 60 capsules.

Store below 30°C.

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
A.B.N. 5000 8422 348
38-42 Wharf Road
WEST RYDE NSW 2114

POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Medicine)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

27 September 2013

DATE OF MOST RECENT AMENDMENT

11 March 2014

® Registered trademark