APPROVED PACKAGE INSERT

SCHEDULING STATUS: S4

PROPRIETARY NAMES AND DOSAGE FORM:

XALKORI® 200 mg capsule

XALKORI® 250 mg capsule

COMPOSITION:

XALKORI 200 mg capsule: Each capsule contains 200 mg crizotinib.

XALKORI 250 mg capsule: Each capsule contains 250 mg crizotinib.

Excipients: Colloidal silicon dioxide, microcrystalline cellulose, anhydrous dibasic calcium phosphate, sodium starch glycolate, magnesium stearate and hard gelatin capsule shells.

The pink opaque capsule shell contains gelatin, titanium dioxide, and red iron oxide.

The white opaque capsule shell contains gelatin and titanium dioxide.

The printing ink contains shellac, propylene glycol, and black iron oxide.

Sugar Free.

PHARMACOLOGICAL CLASSIFICATION:

A 26 Cytostatic agents

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Crizotinib is a selective small-molecule inhibitor of the anaplastic lymphoma kinase (ALK) receptor tyrosine kinase (RTK) and its oncogenic variants (i.e. ALK fusion events and selected ALK mutations). Crizotinib is also an inhibitor of the Hepatocyte Growth Factor Receptor (HGFR, c-Met) RTK, ROS1 (c-ros) and Recepteur d'Origine Nantais (RON) RTKs. Crizotinib demonstrated concentration-dependent inhibition of the kinase activity of ALK, ROS1 and c-Met in biochemical assays and inhibited phosphorylation and modulated kinase-dependent phenotypes in cell-based assays.

Pharmacokinetic properties:

Absorption:

Following oral single dose administration of 250 mg in the fasted state, crizotinib is absorbed with median time to achieve peak concentrations of 4 to 6 hours and the absolute bioavailability was 43 % (range: 32 – 66 %). Following crizotinib 250 mg twice daily, steady state was reached within 15 days and remained stable, with a median accumulation ratio of 4,8.

A high-fat meal reduced crizotinib area-under-the-plasma-concentration versus time curve from time zero to infinity (AUC_{inf}) and maximum observed plasma concentration (C_{max}) by approximately 14 % when a 250 mg single dose was given to healthy volunteers. Therefore, crizotinib can be administered with or without food (see DOSAGE AND DIRECTIONS FOR USE).

Distribution:

The geometric mean volume of distribution (V_{ss}) 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 medicine concentration. *In vitro* studies suggested that crizotinib is a substrate for P-glycoprotein (P-gp). The blood-to-plasma concentration ratio is approximately 1.

Metabolism:

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

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

Elimination:

Following single doses of crizotinib, the apparent plasma terminal half-life 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 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 population groups:

Hepatic insufficiency:

As crizotinib is extensively metabolised in the liver, therefore 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 ALT or AST > 2,5 × ULN or, if due to underlying malignancy, > 5,0 × ULN or with total bilirubin > 1,5 × ULN (see DOSAGE AND DIRECTIONS FOR USE, Table 2 and WARNINGS AND SPECIAL PRECAUTIONS). The population pharmacokinetic analysis using the data from these studies indicated that baseline total bilirubin or AST levels did not have a clinically meaningful effect on the pharmacokinetics of crizotinib.

Renal insufficiency:

No starting dose adjustment is needed for patients with mild (60 ≤ creatinine clearance [Cl_{cr}] < 90 ml/min) or moderate (30 ≤ Cl_{cr} < 60 ml/min) renal impairment, since the population pharmacokinetic analysis indicated no clinically meaningful changes in steady-state XALKORI exposure in these patients. XALKORI plasma concentrations may be increased in patients with severe renal impairment (Cl_{cr} < 30 ml/min). The XALKORI dose should be adjusted to 250 mg taken orally once daily in patients with severe renal impairment not requiring peritoneal dialysis or 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 WARNINGS AND SPECIAL PRECAUTIONS and DOSAGE AND DIRECTIONS FOR USE, Dose modification).

INDICATIONS:

XALKORI is indicated for the treatment of 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.

WARNINGS AND SPECIAL PRECAUTIONS:

Hepatotoxicity:

Safety and efficacy in patients with hepatic impairment have not been studied.

Drug-induced hepatotoxicity with fatal outcome have been reported. Concurrent elevations in ALT and/or AST ≥ 3 × ULN and total bilirubin ≥ 2 × ULN without significant elevations of alkaline phosphatase (≤ 2 × ULN) have been observed in less than 1 % of patients treated with crizotinib. Increases to Grade 3 or 4 ALT or AST elevations were observed in 184 (11 %) and 93 (6 %) of patients respectively. Seventeen (1 %) patients required permanent discontinuation from treatment associated with elevated transaminases, suggesting that these events were generally manageable by dosing modifications as defined in Table 2 (see DOSAGE AND DIRECTIONS FOR USE). Transaminase elevations generally occurred within the first 2 months of treatment. Liver function tests including ALT, AST and total bilirubin should be monitored every 2 weeks during the first 2 months of treatment, then once a month and as clinically indicated, with more frequent repeat testing for Grades 2, 3 or 4 elevations. For patients who develop transaminase elevations, see Dose modification section (see DOSAGE AND DIRECTIONS FOR USE).

Interstitial lung disease (pneumonitis):

XALKORI has been associated with severe, life-threatening or fatal interstitial lung disease (ILD)/pneumonitis in clinical trials at a frequency of 26 (2 %) of 1669 patients treated with XALKORI.

These cases generally occurred within 3 months after the initiation of treatment. Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis. Other potential causes of ILD/pneumonitis should be excluded. XALKORI should be permanently discontinued in patients diagnosed with treatment-related ILD/pneumonitis (see DOSAGE AND DIRECTIONS FOR USE).

QT interval prolongation:

XALKORI can cause QTc prolongation which predispose to severe dysrhythmias. 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 Dose modification section (see DOSAGE AND DIRECTIONS FOR USE and PHARMACOLOGICAL ACTION, Pharmacokinetic properties).

Bradycardia:

Bradycardia has been reported in clinical studies, and it was usually asymptomatic. The full effect of XALKORI on pulse rate may not develop until several weeks after start of treatment. Avoid using XALKORI in combination with other bradycardic medicines (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, XALKORI should be held and the use of concomitant medications should be re-evaluated. For management of patients who develop symptomatic bradycardia, see Dose modification section (see DOSAGE AND DIRECTIONS FOR USE) and Description of selected adverse reactions, Bradycardia section (see SIDE EFFECTS).

Renal impairment:

If patients have severe renal impairment not requiring peritoneal dialysis or haemodialysis, the dose of XALKORI should be adjusted (see DOSAGE AND DIRECTIONS FOR USE and PHARMACOLOGICAL ACTION, Pharmacokinetic properties).

Effects on ability to drive and use machines:

No studies on the effect of XALKORI on the ability to drive and use machines have been performed. However, caution should be exercised when driving or operating machinery because XALKORI causes vision disturbances, dizziness and fatigue (see SIDE EFFECTS).

INTERACTIONS:

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

Medicines that may increase XALKORI plasma concentrations:

Coadministration of XALKORI with strong CYP3A inhibitors may increase XALKORI plasma concentrations. The concomitant use of strong CYP3A inhibitors, including but not limited to atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin and voriconazole should be avoided. Grapefruit or grapefruit juice may also increase plasma concentrations of XALKORI and should be avoided.

Medicines that may decrease XALKORI plasma concentrations:

Coadministration of XALKORI with strong CYP3A inducers may decrease XALKORI plasma concentrations. The concurrent use of strong CYP3A inducers, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin and St. John's wort should be avoided.

Medicines whose plasma concentrations may be altered by XALKORI:

XALKORI has been identified as an inhibitor of CYP3A both *in vitro* and *in vivo*. Caution should be exercised in administering XALKORI in combination with medicines 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 XALKORI 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:

Crizotinib has been identified as an inhibitor of CYP3A both *in vitro* and *in vivo*. Following 28 days of crizotinib dosing at 250 mg taken twice daily in cancer patients, the oral midazolam AUC was 3,7-fold (90 % CI: 2,63 - 5,07) those seen when midazolam was administered alone, suggesting that crizotinib is a moderate inhibitor of CYP3A.

Coadministration of crizotinib and CYP3A inhibitors:

Coadministration of a single 150 mg oral dose of crizotinib in the presence of ketoconazole (200 mg twice daily), a strong CYP3A inhibitor, resulted in increases in crizotinib systemic exposure, with crizotinib AUC_{inf} and C_{max} values that were approximately 3,2-fold and 1,4-fold respectively, those seen when crizotinib was administered alone. However, the magnitude of effect of CYP3A inhibitors on steady-state crizotinib exposure has not been established.

Coadministration of crizotinib and CYP3A inducers:

Coadministration of crizotinib (250 mg twice daily) with rifampin (600 mg once daily), a strong CYP3A inducer, resulted in 84 % and 79 % decreases in crizotinib steady-state AUC_{tau} and $C_{max,}$ respectively, compared to when crizotinib was given alone.

Coadministration of crizotinib with medicines that increase gastric pH:

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

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 medicines 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 medicines that are predominantly metabolised by CYP2B6.

In vitro studies in human hepatocytes indicated that clinical interactions are unlikely to occur as a result of crizotinib-mediated induction of the metabolism of medicines that are substrates for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A.

PREGNANCY AND LACTATION:

Pregnancy:

XALKORI is contraindicated in pregnancy and lactation.

There are no adequate and well-controlled studies in pregnant women using XALKORI. Women of childbearing potential should be advised to avoid becoming pregnant while receiving XALKORI. Women of childbearing potential who are receiving XALKORI, or partners of women of childbearing potential receiving XALKORI, should use adequate contraceptive methods during therapy and for at least 90 days after completing therapy.

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

Lactation:

It is not known whether XALKORI and its metabolites are excreted in human milk. Women using XALKORI should not breastfeed their infants.

Fertility:

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

DOSAGE AND DIRECTIONS FOR USE:

ALK testing:

Detection of ALK-positive NSCLC is necessary for selection of patients for treatment with XALKORI 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 PHARMACOLOGICAL ACTION, Pharmacokinetic properties). Capsules should be swallowed whole. 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 dose to 250 mg taken orally once daily. Dose reduction guidelines for haematologic and non-haematologic toxicities are provided in Table 1 and Table 2.

Table 1: XALKORI 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. National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events. c. In case of recurrence, withhold until recovery to Grade ≤ 2, then resume at 250 mg, once daily. Permanently discontinue in case of further Grade 4 recurrence.	

Table 2: XALKORI dose modification – non-haematologic toxicities:

CTCAE[a] grade	**XALKORI dosing**
Grade 3 or 4 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation with Grade ≤ 1 total bilirubin	Withhold until recovery to Grade ≤ 1 or baseline, then resume at 200 mg twice daily[b]
Grade 2, 3 or 4 ALT or AST elevation with concurrent Grade 2, 3 or 4 total bilirubin elevation (in the absence of cholestasis or 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

CTCAE[a] grade	**XALKORI dosing**
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 antihypertensive medications. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at previous dose upon recovery to Grade ≤ 1 or to heart rate of 60 bpm or above. If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, resume at reduced dose 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 XALKORI is extensively metabolised in the liver, hepatic impairment is likely to increase plasma XALKORI concentrations. However, XALKORI has not been studied in patients with hepatic impairment. Clinical studies that were conducted excluded patients with ALT or AST > 2,5 × ULN or, if due to underlying malignancy, > 5,0 × ULN or with total bilirubin > 1,5 × ULN. Treatment with XALKORI should be used with caution in patients with hepatic impairment (see Table 2 above and WARNINGS AND SPECIAL PRECAUTIONS).

Renal impairment:

No starting dose adjustment is needed for patients with mild (60 ≤ creatinine clearance [Cl_{cr}] < 90 ml/min) or moderate (30 ≤ Cl_{cr} < 60 ml/min) renal impairment, since the population pharmacokinetic analysis indicated no clinically meaningful changes in steady-state XALKORI exposure in these patients.

XALKORI plasma concentrations may be increased in patients with severe renal impairment (Cl_{cr} < 30 ml/min). The XALKORI dose should be adjusted to 250 mg taken orally once daily in patients with severe renal impairment not requiring peritoneal dialysis or 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 WARNINGS AND SPECIAL PRECAUTIONS and PHARMACOLOGICAL ACTION, Pharmacokinetic properties).

Paediatric patients:

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

Elderly:

No starting dose adjustment is required (see PHARMACOLOGICAL ACTION, Pharmacodynamic properties and Pharmacokinetic properties).

SIDE EFFECTS:

Summary of safety profile:

The data described below reflect exposure to XALKORI in 1669 patients with ALK-positive advanced NSCLC who participated in randomised Phase 3 Studies 1007 or 1014 or in single-arm Studies 1001

or 1005. These patients received a starting oral dose of 250 mg twice daily continuously. In Study 1014, the median duration of study treatment was 47 weeks for patients in the XALKORI arm (n = 171); the median duration of treatment was 23 weeks for patients who crossed over from the chemotherapy arm to receive XALKORI treatment (n = 109). In Study 1007, the median duration of study treatment was 48 weeks for patients in the XALKORI arm (n = 172). In ALK-positive NSCLC patients in study 1001 (n = 154), the median duration of treatment was 57 weeks. In Study 1005 (n = 1063), the median duration of treatment was 45 weeks.

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

In 1669 patients treated with XALKORI, all-causality adverse events associated with dosing interruptions or dose reductions occurred in 739 (44 %) and 253 (15 %) patients respectively. All-causality adverse events associated with permanent treatment discontinuation occurred in 298 (18 %) patients.

The adverse drug reactions listed in the table below are presented by System Organ Class (SOC) and frequency categories, defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100) or rare (≥ 1/10 000 to < 1/1 000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 3: Adverse drug reactions for XALKORI:

System Organ Class	**Very Common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1 000 to < 1/100**
Blood and lymphatic system disorders	Neutropenia[a], leucopenia[b]		

System Organ Class	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1 000 to < 1/100
Metabolism and nutrition disorders	Decreased appetite		
Nervous system disorders	Neuropathy[c], dizziness[d], dysgeusia		
Eye disorders	Vision disorder[e]		
Cardiac disorders	Bradycardia[f]	Electrocardiogram QT prolonged, syncope	
Respiratory, thoracic and mediastinal disorders		Interstitial lung disease[g]	
Gastrointestinal disorders	Vomiting, diarrhoea, nausea, constipation	Dyspepsia	
Hepatobiliary disorders	Elevated transaminases[h]	Increased blood alkaline phosphatase	Hepatic failure
Skin and subcutaneous tissue disorders	Rash		
Renal and urinary disorders		Renal cyst[i], Increased blood creatinine[j]	
General disorders and administration site conditions	Oedema[k] Fatigue		

Terms actually reported in the studies up to the data cutoff date and contributing to the relevant adverse reaction are indicated in parentheses, as listed below.

a. Neutropenia (febrile neutropenia, neutropenia, decreased neutrophil count).

System Organ Class	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1 000 to < 1/100
b. Leucopenia (leucopenia, decreased white blood cell count). c. Neuropathy (burning sensation, dysaesthesia, formication, gait disturbance, hyperaesthesia, hypoaesthesia, hypotonia, motor dysfunction, muscle atrophy, muscular weakness, neuralgia, neuritis, peripheral neuropathy, neurotoxicity, paraesthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, peroneal nerve palsy, polyneuropathy, sensory disturbance, skin burning sensation). d. Dizziness (balance disorder, dizziness, postural dizziness, presyncope). e. Vision disorder (diplopia, halo vision, photophobia, photopsia, blurred vision, reduced visual acuity, visual brightness, visual field defect, visual impairment, vitreous floaters). f. Bradycardia (bradycardia, decreased heart rate, sinus bradycardia). g. Interstitial lung disease (acute respiratory distress syndrome, alveolitis, interstitial lung disease, pneumonitis). h. Elevated transaminases (increased alanine aminotransferase, increased aspartate aminotransferase, increased gamma-glutamyltransferase, increased hepatic enzyme, abnormal hepatic function, abnormal liver function test, increased transaminases). i. Renal cyst (renal abscess, renal cyst, renal cyst haemorrhage, renal cyst infection). j. Increased blood creatinine (increased blood creatinine, decreased creatinine renal clearance). k. Oedema (face oedema, generalised oedema, local swelling, localised oedema, oedema, peripheral oedema, periorbital oedema).			

Event terms that represent the same medical concept or condition were grouped together and reported as a single adverse reaction in the table above.

Description of selected adverse reactions:

Visual effects:

In clinical trials of patients with ALK-positive advanced NSCLC, all-causality vision disorder, most commonly visual impairment, photopsia, blurred vision and vitreous floaters, was experienced by 1038 (62 %) of 1669 patients treated with XALKORI. Ninety-five percent of these patients had events

that were mild in severity. Ophthalmological evaluation should be considered if vision disorder persists or worsens in severity. Seven (0,4 %) patients had temporary treatment discontinuation and 2 (0,1 %) patients had a dose reduction associated with vision disorder. There were no permanent discontinuations associated with vision disorder for any of the 1669 patients treated with XALKORI.

Based on the Visual Symptom Assessment Questionnaire (VSAQ-ALK), patients treated with XALKORI in Study 1007 and Study 1014 reported a higher incidence of visual disturbances compared to patients treated with chemotherapy. The onset of vision disorder generally occurred during the first week of medicine administration. The majority of patients in the XALKORI arms in Study 1007 and Study 1014 (> 50 %) reported visual disturbances, which occurred at a frequency of 4 to 7 days each week, lasted up to 1 minute, and had mild or no impact (scores 0 to 3 out of a maximum score of 10) on daily activities as captured by the VSAQ-ALK questionnaire.

Gastrointestinal effects:

Nausea (57 %), diarrhoea (54 %), vomiting (51 %) and constipation (43 %) were the most commonly reported all-causality gastrointestinal events. Median times to onset for nausea and vomiting were 4 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:

All-causality neuropathy, as defined in Table 3, was experienced by 419 (25 %) of 1669 patients treated with XALKORI, and was primarily Grade 1 or 2 in severity. Dizziness and dysgeusia were also very commonly reported and were primarily Grade 1 in severity.

Bradycardia:

In clinical trials of patients with ALK-positive advanced NSCLC, all-causality bradycardia was experienced by 205 (12 %) of 1669 patients treated with XALKORI. Most events were mild in severity.

A total of 242 (15 %) 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 Dose modification section (see DOSAGE AND DIRECTIONS FOR USE) and Bradycardia section (see WARNINGS AND SPECIAL PRECAUTIONS).

Renal cyst:

All-causality complex renal cysts were experienced by 50 (3 %) of 1669 patients treated with XALKORI. 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:

Haematologic laboratory abnormalities:

In clinical studies of XALKORI in patients with ALK-positive advanced NSCLC, shifts to Grade 3 or 4 decreases in leucocytes and neutrophils were observed in 63 (4 %) and 221 (14 %) patients respectively. Complete blood counts including differential white blood cell counts should be monitored as clinically indicated, with more frequent repeat testing if Grade 3 or 4 abnormalities are observed, or if fever or infection occurs. In patients who develop haematologic laboratory abnormalities, see Dose modification section (see DOSAGE AND DIRECTIONS FOR USE).

Hepatic laboratory abnormalities:

In clinical studies of XALKORI in patients with ALK-positive advanced NSCLC, shifts to Grade 3 or 4 ALT, AST and alkaline phosphatase were observed in 184 (11 %), 93 (6 %), and 33 (2 %) patients respectively. Patients should be monitored for hepatotoxicity and managed as recommended in Hepatotoxicity section (see WARNINGS AND SPECIAL PRECAUTIONS).

Renal laboratory abnormalities:

In clinical studies of XALKORI in patients with ALK-positive advanced NSCLC, the estimated glomerular filtration rate (eGFR) decreased from a baseline median of 96,42 ml/min/1,73 m^2 (n=1681) to a median of 80,23 ml/min/1,73 m^2 at 2 weeks of treatment (n=1499). Median eGFR appeared to be relatively stable from 12 weeks of treatment (78,06 ml/min/1,73 m^2, n=1338) through 104 weeks of treatment (75,45 ml/min/1,73 m^2, n=315) and increased to 83,02 ml/min/1,73 m^2 at 28 days after the last dose of XALKORI (n=123).

Shifts to eGFR Grade 4 (15 to < 30 ml/min/1,73 m^2) or to eGFR Grade 5 (< 15 ml/min/1,73 m^2) were observed in 3 % and < 1 % of patients, respectively.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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

IDENTIFICATION:

XALKORI 200 mg: Size 1 hard gelatin capsule with pink opaque cap and white opaque body, printed with black ink “Pfizer” on the cap, “CRZ 200” on the body, containing a white to pale yellow powder.

XALKORI 250 mg: Size 0 hard gelatin capsule with pink opaque cap and body, printed with black ink “Pfizer” on the cap, “CRZ 250” on the body; containing a white to pale yellow powder.

PRESENTATION:

Packaged in white HDPE bottles with a white polypropylene closure and aluminium foil/polyethylene inner seal containing 60 hard gelatin capsules or packaged in clear PVC/aluminium foil blisters containing 60 or 100 hard gelatin capsules. The foil blisters are placed in an outer carton.

STORAGE INSTRUCTIONS:

Store at or below 25 °C.

Do not remove blister from carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

XALKORI 200 mg: 47/26/0568

XALKORI 250 mg: 47/26/0569

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATES OF REGISTRATION:

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton 2196

South Africa

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

Date of registration: 20 March 2018

Manufacturer: Pfizer Manufacturing Deutschland GmbH, Freiburg, Germany