SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

XALKORI® 200 mg capsule

XALKORI® 250 mg capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules.

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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

XALKORI is indicated for:

- the treatment of adults with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)

- the treatment of adults with c-ros oncogene 1 (ROS1)-positive advanced non-small cell lung cancer (NSCLC)

4.2 Posology and method of administration

Posology

ALK and ROS1 testing

Detection of either ALK-positive or ROS1-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 either ALK-positive or ROS1-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. Treatment should be stopped when the patient ceases to derive clinical benefit.

XALKORI may be taken with or without food (see section 5.2). 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 for patients treated with XALKORI 250 mg orally twice daily, then the dose of XALKORI should be reduced as below:

- First dose reduction: XALKORI 200 mg taken orally twice daily
- Second dose reduction: XALKORI 250 mg taken orally once daily
- Permanently discontinue if unable to tolerate XALKORI 250 mg taken orally once daily

Dose reduction guidelines for haematologic and non-haematologic toxicities are provided in Table 1 and Table 2. For patients treated with a lower dose of XALKORI than 250 mg twice daily, then follow the dose reduction guidelines provided in Tables 1 and 2 accordingly.

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 the next lower dose [c,d]

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

b. National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE).

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.

d. For patients treated with 250 mg once daily or whose dose was reduced to 250 mg once daily, discontinue during evaluation.

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 the next lower dose[b,c]
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 (ILD)/pneumonitis[d]	Permanently discontinue
Grade 3 QTc prolongation	Withhold until recovery to Grade ≤ 1, then resume at the next lower dose[b,c]
Grade 4 QTc prolongation	Permanently discontinue

Grade 2, 3 bradycardia[e] (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 medicines known to cause bradycardia, as well as antihypertensive medications. If contributing concomitant medicines are 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 medicines are identified, or if contributing concomitant medications are not discontinued or dose modified, resume at reduced dose[c] upon recovery to Grade ≤ 1 or to heart rate of 60 bpm or above.

Grade 4 bradycardia [e,f] (life-threatening consequences, urgent intervention indicated)	Permanently discontinue if no contributing concomitant medicines are identified. If contributing concomitant medicines are 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.
Grade 4 Ocular disorder (Visual loss)	Discontinue during evaluation of severe vision loss

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. See sections 4.4 and 4.8.

c. For patients treated with 250 mg once daily or whose dose was reduced to 250 mg once daily, discontinue during evaluation.

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

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

f. Permanently discontinue for recurrence.

Special populations

Hepatic impairment

XALKORI is extensively metabolised in the liver. Treatment with XALKORI should be used with caution in patients with hepatic impairment (see Table 2 above and sections 4.4, 4.8 and 5.2).

No starting dose adjustment of XALKORI is recommended for patients with mild hepatic impairment (either AST > Upper Limit of Normal (ULN) and total bilirubin ≤ ULN or any AST and total bilirubin > ULN but ≤ 1,5 × ULN). The starting XALKORI dose for patients with moderate hepatic impairment (any AST and total bilirubin > 1,5 × ULN and ≤ 3 × ULN) is recommended to be 200 mg twice daily. The starting XALKORI dose for patients with severe hepatic impairment (any AST and total bilirubin > 3 × ULN) is recommended to be 250 mg once daily.

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 starting 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 sections 4.4 and 5.2).

Elderly

No starting dose adjustment is required.

Paediatric population

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

Method of administration

For oral use.

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

Use of XALKORI is contraindicated in patients with hypersensitivity to crizotinib or to any of the excipients of XALKORI listed in section 6.1.

4.4 Special warnings and precautions for use

Hepatotoxicity

Drug-induced hepatotoxicity with fatal outcome have been reported (see section 4.8). 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 XALKORI.

Increases to Grade 3 or 4 ALT or AST elevations were observed in 187 (11 %) and 95 (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 section 4.2). 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 section 4.2).

Interstitial lung disease (ILD/pneumonitis)

XALKORI has been associated with severe, life-threatening or fatal ILD/pneumonitis in clinical trials at a frequency of 26 (2 %) of 1772 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 section 4.2 and 4.8).

QT interval prolongation

QTc prolongation has been observed in clinical studies in patients treated with XALKORI (see sections 4.8 and 5.2) which may lead to an increased risk for ventricular tachyarrhythmias (e.g., *Torsade de Pointes*) or sudden death. 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, electrolytes and renal function should be considered. For patients who develop QTc prolongation, see Dose modification section (see section~~s~~ 4.2 and 4.8).

Bradycardia

Bradycardia has been reported in clinical studies in 13 % of patients, 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 withheld and the use of concomitant medications should be re-evaluated. For management of patients who develop symptomatic bradycardia, see Dose modifications section (see section 4.2) and Description of selected adverse reactions, Bradycardia section (see section 4.8).

Cardiac failure

In clinical studies with XALKORI and during post marketing surveillance in adult patients, severe, life-threatening, or fatal adverse reactions of cardiac failure were reported (see section 4.8).

Patients with or without pre-existing cardiac disorders, receiving XALKORI, should be monitored for signs and symptoms of heart failure (dyspnoea, oedema, rapid weight gain from fluid retention). Dosing interruption, dose reduction, or discontinuation should be considered as appropriate if such symptoms are observed.

Neutropenia and leukopenia

In clinical studies with XALKORI in adult patients with either ALK-positive or ROS1-positive NSCLC, Grade 3 or 4 neutropenia has been very commonly reported (12 %).Grade 3 or 4 leukopenia has been commonly reported (3 %) in patients with ALK-positive or ROS1-positive NSCLC. Less than 0,5 % of adult patients with either ALK-positive or ROS1-positive NSCLC experienced febrile neutropenia in clinical studies with XALKORI. 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 (see section 4.2).

Gastrointestinal perforation

In clinical studies with XALKORI, events of gastrointestinal perforations were reported. There were reports of fatal cases of gastrointestinal perforation during post-marketing use of XALKORI (see section 4.8).

XALKORI should be used with caution in patients at risk for gastrointestinal perforation (e.g., history of diverticulitis, metastases to the gastrointestinal tract, concomitant use of medicines with a recognised risk of gastrointestinal perforation).

XALKORI should be discontinued in patients who develop gastrointestinal perforation. Patients should be informed of the first signs of gastrointestinal perforations and be advised to consult rapidly in case of occurrence.

Renal effects

Blood creatinine increase and creatinine clearance decreased were observed in patients in clinical studies with XALKORI. Renal failure and acute renal failure were reported in patients treated with XALKORI in clinical studies and during post marketing. Cases with fatal outcome, cases requiring haemodialysis and cases of Grade 4 hyperkalaemia were also observed in adult patients. Monitoring of patients for renal function at baseline and during therapy with XALKORI is recommended, with particular attention to those who have risk factors or previous history of renal impairment (see section 4.8).

Renal impairment

If patients have severe renal impairment not requiring peritoneal dialysis or haemodialysis, the dose of XALKORI should be adjusted (see sections 4.2 and 5.2).

Visual effects

In any patient with new onset of Grade 4 visual loss, XALKORI treatment should be discontinued and ophthalmological evaluation should be performed.

Ophthalmological evaluation is recommended if vision disorder persists or worsens in severity (see section 4.2).

Photosensitivity

Photosensitivity has been reported in patients treated with XALKORI (see section 4.8). Patients should be advised to avoid prolonged sun exposure while taking XALKORI and, when outdoors, to take protective measures (e.g., use of protective clothing and/or sunscreen).

4.5 Interaction with other medicines and other forms of interaction

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

Co-administration 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 concentration

Co-administration 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, rifampicin 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.

Co-administration 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.

Co-administration of XALKORI and CYP3A substrates

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

Co-administration of XALKORI and CYP3A inhibitors

Co-administration of XALKORI (250 mg once daily) with itraconazole (200 mg once daily), a strong CYP3A inhibitor, resulted in 57 % and 33 % increases in XALKORI steady-state area under the plasma concentration-time curve from 0 hour to time tau, the dosing interval (AUC_{tau}) and C_{max}, respectively, compared to when XALKORI was given alone.

Co-administration of XALKORI *and CYP3A inducers*

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

Co-administration of XALKORI *with medicines that increase gastric pH*

The aqueous solubility of XALKORI is pH dependent, with low (acidic) pH resulting in higher solubility. Administration of a single 250 mg XALKORI dose following treatment with esomeprazole 40 mg once daily for 5 days resulted in an approximately 10 % decrease in XALKORI 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 XALKORI is co-administered with medicines that increase gastric pH (such as proton-pump inhibitors, H_2 blockers or antacids).

Co-administration with other CYP substrates

In vitro studies indicated that clinical drug-drug interactions are unlikely to occur as a result of XALKORI-mediated inhibition of the metabolism of medicines that are substrates for CYP1A2, CYP2C8, CYP2C9, CYP2C19 or CYP2D6. XALKORI is an inhibitor of CYP2B6 *in vitro*. Therefore, XALKORI may have the potential to increase plasma concentrations of co-administered 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 XALKORI-mediated induction of the metabolism of medicines that are substrates for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A.

4.6 Fertility, pregnancy and lactation

XALKORI is contraindicated in pregnancy and lactation.

Women of childbearing potential/Contraception in males and females

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.

Pregnancy

XALKORI may cause foetal harm when administered to a pregnant woman. 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.

Breastfeeding

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 non-clinical safety findings, male and female fertility may be compromised by treatment with XALKORI.

4.7 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 section 4.8).

4.8 Undesirable effects

Summary of the 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 and in 53 patients with ROS1-positive advanced NSCLC who participated in single-arm Study 1001, for a total of 1722 patients. 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. For ROS1-positive NSCLC patients in Study 1001 (n=53), the median duration of treatment was 101 weeks.

The most serious adverse reactions in 1722 patients with either ALK-positive or ROS1-positive advanced NSCLC were hepatotoxicity, ILD/pneumonitis and QT interval prolongation (see section 4.4). The most common adverse reactions (≥ 25 %) in patients with either ALK-positive or ROS1-positive NSCLC were vision disorder, nausea, diarrhoea, vomiting, oedema, constipation, elevated transaminases, decreased appetite, fatigue, dizziness and neuropathy.

In 1722 patients with either ALK-positive or ROS1-positive NSCLC treated with XALKORI, all-causality adverse events associated with dosing interruptions or dose reductions occurred in 763 (44 %) and 259 (15 %) patients respectively. All-causality adverse events associated with permanent treatment discontinuation occurred in 302 (18 %) patients.

The adverse drug reactions listed in the Table 3 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	Frequency	Side effect
Blood and lymphatic system disorders	Very common	Neutropenia[a], anaemia[b], leukopenia[c]
Metabolism and nutrition disorders	Very common	Decreased appetite
	Common	Hypophosphataemia
Nervous system disorders	Very common	Neuropathy[d], dizziness[f], dysgeusia
Eye disorders	Very common	Vision disorder[e]
Cardiac disorders	Very common	Bradycardia[g]
	Common	Cardiac failure[h], prolonged electrocardiogram QT, syncope
Respiratory, thoracic and mediastinal disorders	Common	Interstitial lung disease[i]
Gastrointestinal disorders	Very common	Vomiting, diarrhoea, nausea, constipation, abdominal pain[j]
	Common	Oesophagitis[k], dyspepsia
	Uncommon	Gastrointestinal perforation[l]
	Very common	Elevated transaminases[m]

Hepato-biliary disorders	Common	Increased blood alkaline phosphatase
	Uncommon	Hepatic failure
Skin and subcutaneous tissue disorders	Very common	Rash
	Uncommon	Photosensitivity
Renal and urinary disorders	Common	Renal cyst[n], increased blood creatinine[o]
	Uncommon	Acute renal failure, renal failure
General disorders and administration site conditions	Very common	Oedema[p], fatigue
Investigations	Common	Decreased blood testosterone[q]
	Uncommon	Increased blood phosphokinase

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).

b. Anaemia (anaemia, haemoglobin decreased, hypochromic anaemia).

c. Leukopenia (leukopenia, decreased white blood cell count).

d. 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).

e. Vision disorder (diplopia, halo vision, photophobia, photopsia, blurred vision, reduced visual acuity, visual brightness, visual field defect, visual impairment, vitreous floaters).

f. Dizziness (balance disorder, dizziness, postural dizziness, presyncope).

g. Bradycardia (bradycardia, decreased heart rate, sinus bradycardia).

h. Cardiac failure (cardiac failure, cardiac failure congestive, ejection fraction decreased, left ventricular failure, pulmonary oedema). Across clinical studies (n=1722), 19 (1,1 %) patients treated with XALKORI had any grade cardiac failure, 8 (0,5 %) patients had Grade 3 or 4, and 3 (0,2 %) patients had fatal outcome.

i. Interstitial lung disease (acute respiratory distress syndrome, alveolitis, interstitial lung disease, pneumonitis).

j. Abdominal pain (abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness).

k. Oesophagitis (oesophagitis, oesophageal ulcer).

l. Gastrointestinal perforation (gastrointestinal perforation, intestinal perforation, large intestine perforation).

m. Elevated transaminases (increased alanine aminotransferase, increased aspartate aminotransferase, increased gamma-glutamyltransferase, increased hepatic enzyme, abnormal hepatic function, abnormal liver function test, increased transaminases).

n. Renal cyst (renal abscess, renal cyst, renal cyst haemorrhage, renal cyst infection).

o. Increased blood creatinine (increased blood creatinine, decreased creatinine renal clearance).

p. Oedema (face oedema, generalised oedema, local swelling, localised oedema, oedema, peripheral oedema, periorbital oedema).

q. Decreased blood testosterone (decrease blood testosterone, hypogonadism, secondary hypogonadism).

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 either ALK-positive or ROS1-positive advanced NSCLC, all-causality vision disorder, most commonly visual impairment, photopsia, blurred vision and vitreous floaters, was

experienced by 1084 (63 %) of 1722 patients treated with XALKORI. Of the 1084 patients who experienced vision disorder, 95 % 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 1722 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

Supportive care should include the use of antiemetic medicines. For additional supportive care for paediatric patients, see section 4.4.

Adult patients with NSCLC

Nausea (57 %), diarrhoea (54 %), vomiting (51 %) and constipation (43 %) were the most commonly reported all-causality gastrointestinal events in adult patients with either ALK-positive or ROS1-positive NSCLC. Most events were mild to moderate in severity. Median times to onset for nausea and vomiting were 3 days and these events declined in frequency after 3 weeks of treatment. In clinical trials, the most commonly used antiemetic medicines were ondansetron and prochlorperazine. Median times to onset for diarrhoea and constipation were 13 and 17 days, respectively. Supportive care for diarrhoea and constipation should include the use of standard anti-diarrhoeal and laxative medicines respectively.

In clinical studies of adult patients with NSCLC treated with XALKORI, events of gastrointestinal perforations were reported. There were reports of fatal cases of gastrointestinal perforation during post-marketing use of XALKORI (see section 4.4).

QT interval prolongation

QT prolongation can result in arrhythmias and is a risk factor for sudden death. QT prolongation may clinically manifest as bradycardia, dizziness, and syncope. Electrolyte disturbances, dehydration and bradycardia may further increase the risk of QTc prolongation and thus, periodic monitoring of ECG and electrolyte levels is recommended in patients with GI toxicity (see section 4.4).

Adult patients with NSCLC

Across studies in adult patients with either ALK -positive or ROS1 positive advanced NSCLC, QTcF (corrected QT by the Fridericia method) ≥ 500 msec was recorded in 34 (2,1 %) of 1619 patients with at least 1 postbaseline ECG assessment and a maximum increase from baseline in QTcF ≥ 60 msec was observed in 79 (5,0 %) of 1585 patients with a baseline and at least 1 postbaseline ECG assessment. All causality Grade 3 or 4 Electrocardiogram QT prolonged was reported in 27 (1,6 %) out of 1722 patients (see sections 4.2, 4.4, 4.5 and 5.2).

In a single arm ECG substudy in adult patients (see section 5.2) using blinded manual ECG measurements 11 (21 %) patients had an increase from Baseline in QTcF value ≥ 30 to < 60 msec and 1 (2 %) patient had an increase from Baseline in QTcF value of ≥ 60 msec. No patients had a maximum QTcF ≥ 480 msec. The central tendency analysis indicated that the largest mean change from baseline in QTcF was 12,3 msec (95 % CI 5,1 19,5 msec, least squares mean [LS] from Analysis of Variance [ANOVA]) and occurred at 6 hours post dose on Cycle 2 Day 1. All upper limits of the 90 % CI for the LS mean change from Baseline in QTcF at all Cycle 2 Day 1 time points were < 20 msec.

Nervous system effects

All-causality neuropathy, as defined in Table 3, was experienced by 435 (25 %) of 1722 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 either ALK-positive or ROS1-positive advanced NSCLC, all-causality bradycardia was experienced by 219 (13 %) of 1722 patients treated with XALKORI. Most events were mild in severity. A total of 259 (16 %) of 1666 patients with at least 1 post-baseline vital sign assessment 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 section 4.2) and Bradycardia section (see section 4.4).

Interstitial lung disease/pneumonitis

Patients with pulmonary symptoms indicative of ILD/pneumonitis should be monitored. Other potential causes of ILD/pneumonitis should be excluded (see sections 4.2 and 4.4).

Adult patients with NSCLC

Severe, life-threatening, or fatal ILD/pneumonitis can occur in patients treated with XALKORI. Across studies in adult patients with either ALK-positive or ROS1-positive NSCLC (N=1722), 50 (3 %) patients treated with XALKORI had any grade all-causality ILD, including 18 (1 %) patients with Grade 3 or 4, and 8 (< 1 %) patients with fatal cases. According to an independent review committee (IRC) assessment of patients with ALK-positive NSCLC (N=1 669), 20 (1,2 %) patients had ILD/pneumonitis, including 10 (< 1 %) patients with fatal cases. These cases generally occurred within 3 months after the initiation of treatment.

Renal cyst

All-causality complex renal cysts were experienced by 52 (3 %) of 1722 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 either ALK-positive or ROS1-positive advanced NSCLC, shifts to Grade 3 or 4 decreases in leukocytes and neutrophils were observed in 64 (4 %) and 226 (13 %) 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 section 4.2).

Hepatic laboratory abnormalities

In clinical studies of XALKORI in patients with either ALK-positive or ROS1-positive advanced NSCLC, shifts to Grade 3 or 4 ALT, AST and alkaline phosphatase were observed in 187 (11 %), 95 (6 %), and 33 (2 %) patients, respectively. Patients should be monitored for hepatotoxicity and managed as recommended in Hepatotoxicity section (see section 4.4).

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 26 Cytostatic agents

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. The anti-tumour efficacy of crizotinib was dose-dependent and demonstrated a correlation with inhibition of ROS1 phosphorylation *in vivo*.

5.2 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 section 4.2).

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.

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 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 radio-labelled 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 auto-inhibition of CYP3A by crizotinib after multiple dosing.

Special populations

Hepatic impairment

Crizotinib is extensively metabolised in the liver. Patients with mild (either AST > ULN and total bilirubin ≤ ULN or any AST and total bilirubin > ULN but ≤ 1,5 × ULN), moderate (any AST and total bilirubin > 1,5 × ULN and ≤ 3×ULN), or severe (any AST and total bilirubin > 3 × ULN) hepatic impairment or normal (AST and total bilirubin ≤ ULN) hepatic function, who were matched controls for mild or moderate hepatic impairment, were enrolled in an open-label, non-randomised clinical study (Study 1012), based on NCI classification.

Following crizotinib 250 mg twice daily dosing, patients with mild hepatic impairment (n=10) showed similar systemic crizotinib exposure at steady state compared to patients with normal hepatic function (n=8), with geometric mean ratios for area under the plasma concentration-time curve as daily exposure at steady state (AUC_{daily}) and C_{max} of 91,1 % and 91,2 %, respectively. No starting dose adjustment is recommended for patients with mild hepatic impairment.

Following crizotinib 200 mg twice daily dosing, patients with moderate hepatic impairment (n=8) showed higher systemic crizotinib exposure compared to patients with normal hepatic function (n=9) at the same dose level, with geometric mean ratios for AUC_{daily} and C_{max} of 150 % and 144 %, respectively. However, the systemic crizotinib exposure in patients with moderate hepatic impairment at the dose of

200 mg twice daily was comparable to that observed from patients with normal hepatic function at a dose of 250 mg twice daily, with geometric mean ratios for AUC_{daily} and C_{max} of 114 % and 109 %, respectively.

The systemic crizotinib exposure parameters AUC_{daily} and C_{max} in patients with severe hepatic impairment (N=6) receiving a crizotinib dose of 250 mg once daily were approximately 64,7 % and 72,6 %, respectively, of those from patients with normal hepatic function receiving a dose of 250 mg twice daily.

An adjustment of the dose of crizotinib is recommended when administering crizotinib to patients with moderate or severe hepatic impairment (see sections 4.2 and 4.4).

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 crizotinib exposure in these patients. Crizotinib plasma concentrations may be increased in patients with severe renal impairment (Cl_{cr} < 30 mL/min). 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 sections 4.4 and 4.2, Dose modification).

Age

Based on the population pharmacokinetic analysis of data from the relevant studies conducted, age has no effect on crizotinib pharmacokinetics (see section 4.2).

Body weight and gender

Based on the population pharmacokinetic analysis of data from the relevant studies conducted, there was no clinically meaningful effect of body weight or gender on crizotinib pharmacokinetics.

Ethnicity

Based on the population pharmacokinetic analysis of data from the relevant studies conducted, the predicted area under the plasma concentration-time curve at steady-state (AUC_{ss}) (95 % CI) was 23 % - 37 % higher in Asian patients (N=523) than in non-Asian patients (N=691).

In studies in patients with ALK-positive advanced NSCLC (N=1669), the following adverse reactions were reported with an absolute difference of ≥ 10 % in Asian patients (N=753) than in non-Asian patients (N=916): elevated transaminases, decreased appetite, neutropenia, and leukopenia. No adverse medicine reactions were reported with an absolute difference of ≥ 15 %.

Geriatric

Limited data are available in this subgroup of patients (see section 4.2). Based on the population pharmacokinetic analysis of data from the relevant studies conducted, age has no effect on crizotinib pharmacokinetics.

Cardiac electrophysiology

The QT interval prolongation potential of crizotinib was assessed in patients with either ALK-positive or ROS1-positive NSCLC 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. Thirty-four of 1619 patients (2,1 %) with at least 1 postbaseline ECG assessment were found to have QTcF ≥ 500 msec, and 79 of 1585 patients (5,0 %) with a baseline and at least 1 postbaseline ECG assessment had an increase from baseline QTcF ≥ 60 msec by automated machine-read evaluation of ECG (see section 4.4).

An ECG substudy using blinded manual ECG measurements was conducted in 52 ALK-positive NSCLC patients who received crizotinib 250 mg twice daily. Eleven (21 %) patients had an increase from Baseline in QTcF value ≥ 30 to < 60 msec and 1 (2 %) patient had an increase from Baseline in QTcF value of ≥ 60 msec. No patients had a maximum QTcF ≥ 480 msec. The central tendency

analysis indicated that all upper limits of the 90 % CI for the LS mean change from Baseline in QTcF at all Cycle 2 Day 1 time points were < 20 msec. A pharmacokinetic/pharmacodynamic analysis suggested a relationship between crizotinib plasma concentration and QTc. In addition, a decrease in heart rate was found to be associated with increasing crizotinib plasma concentration (see section 4.4), with a maximum mean reduction of 17.8 beats per minute (bpm) after 8 hours on Cycle 2 Day 1.

5.3 Preclinical safety data

In rat and dog repeat-dose toxicity studies up to 3-month duration, the primary target organ effects were related to the gastrointestinal (emesis, faecal changes, congestion), haematopoietic (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 2,6-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 1,8-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 1,1-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. Post-implantation loss was increased at doses ≥ 50 mg/kg/day (approximately 0,4 times the AUC at the recommended human dose) in rats, and reduced foetal body weights were considered adverse effects in the rat and rabbit at 200 and 60 mg/kg/day, respectively (approximately 1,2-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 3,3 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

Colloidal silicon dioxide

Microcrystalline cellulose

Anhydrous dibasic calcium phosphate

Sodium starch glycolate

Magnesium stearate

Hard gelatin capsule:

- 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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Do not remove blister from carton until required for use.

6.5 Nature and contents of container

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.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton 2196

South Africa

Tel: +27(0)11 320 6000 / 0860 734 937 (Toll-free South Africa)

8. REGISTRATION NUMBERS

XALKORI 200 mg: 47/26/0568

XALKORI 250 mg: 47/26/0569

9. DATE OF FIRST AUTHORISATION

20 March 2018

10. DATE OF REVISION OF THE TEXT

15 January 2024

Manufacturer: Pfizer Manufacturing Deutschland GmbH, Freiburg, Germany