This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

XALKORI®▽(crizotinib) Therapeutic Management Guide

Physicians prescribing XALKORI® should:

- review this Therapeutic Management Guide and the full Product Information for XALKORI®.
- review the Patient Booklet and Patient Alert Card and explain their role and use to patients who will receive XALKORI®. The patient should be provided with the Patient Booklet and Patient Alert Card with each prescription.

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

XALKORI® is indicated for the treatment of adults with previously treated anaplastic lymphoma kinase (ALK)-positive advanced NSCLC. [1]

See back cover for full prescribing information.

Reference: 1. XALKORI® Summary of Product Characteristics. MMMM 2015.
PF-L-2015-144. August 2015.

Pfizer Oncology

XALKORI® CRIZOTINIB

XALKORI® DOSING

ALK-POSITIVE NSCLC STATUS SHOULD BE ESTABLISHED PRIOR TO INITIATION OF XALKORI® THERAPY. AN ACCURATE AND VALIDATED ALK ASSAY IS NECESSARY FOR THE SELECTION OF PATIENTS FOR TREATMENT WITH XALKORI®.

The standard dose schedule of XALKORI®
is 250 mg taken orally twice daily continuously[1]

AM*

PM*

Standard dose: 500 mg/day[1]

*Capsule not shown in actual size.

ALK = anaplastic lymphoma kinase; NSCLC = non-small-cell lung cancer.

Reference: 1. XALKORI® Summary of Product Characteristics. MMMM 2015.

ADVERSE REACTIONS REPORTED WITH **XALKORI®**

DATA DESCRIBED BELOW REFLECT EXPOSURE TO XALKORI® IN 1,669 PATIENTS WITH ALK-POSITIVE ADVANCED NSCLC WHO PARTICIPATED IN 2 RANDOMISED PHASE 3 STUDIES (PROFILE 1007 AND PROFILE 1014) AND 2 SINGLE-ARM STUDIES (PROFILE 1005 AND PROFILE 1001).

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] (22%) Anaemia[b] (15%) Leukopenia[c] (15%)		
Metabolism and nutrition disorders	Decreased appetite (30%)	Hypophosphataemia (6%)	
Nervous system disorders	Neuropathy[d] (25%) Dysgeusia (21%)		
Eye disorders	Vision disorder[e] (62%)		
Cardiac disorders	Dizziness[f] (25%) Bradycardia[g] (12%)	Electrocardiogram QT prolonged (4%) Syncope (3%)	
Respiratory, thoracic and mediastinal disorders		Interstitial Lung Disease[h] (3%)	
Gastrointestinal disorders	Vomiting (51%) Diarrhoea (54%) Nausea (57%) Constipation (43%) Abdominal pain[i] (21%)	Dyspepsia (8%)	Gastrointestinal perforation[j] (<1%)
Hepatobiliary disorders	Elevated transaminases[k] (32%)	Blood alkaline phosphatase increased (7%)	Hepatic failure (<1%)
Skin and subcutaneous tissue disorders	Rash (13%)		
Renal and urinary disorders		Renal cyst[l] (3%)	
General disorders and administration site conditions	Oedema[m] (49%) Fatigue (30%)		

Includes cases reported within the clustered terms: [a]Neutropenia (Febrile neutropenia, Neutropenia, Neutrophil count decreased). [b]Anaemia (Anaemia, Haemoglobin decreased, Hypochromic anaemia). [c]Leukopenia (Leukopenia, White blood cell count decreased). [d]Neuropathy (Burning sensation, Dysaesthesia, Formication, Gait disturbance, Hyperaesthesia, Hypoaesthesia, Hypotonia, Motor dysfunction, Muscle atrophy, Muscular weakness, Neuralgia, Neuritis, Neuropathy peripheral, 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, Vision blurred, Visual acuity reduced, Visual brightness, Visual field defect, Visual impairment, Vitreous floaters). [f]Dizziness (Balance disorder, Dizziness, Dizziness postural, Presyncope). [g]Bradycardia (Bradycardia, Heart rate decreased, Sinus bradycardia). [h]Interstitial Lung Disease (Acute respiratory distress syndrome, Alveolitis, Interstitial lung disease, Pneumonitis). [i]Abdominal pain (Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness). [j]Gastrointestinal Perforation (Gastrointestinal perforation, Intestinal perforation). [k]Elevated Transaminases (Alanine aminotransferase increased, Aspartate aminotransferase increased, Gamma-glutamyltransferase increased, Hepatic enzyme increased, Hepatic function abnormal, Liver function test abnormal, Transaminases increased). [l]Renal Cyst (Renal abscess, Renal cyst, Renal cyst haemorrhage, Renal cyst infection). [m]Oedema (Face oedema, Generalised oedema, Local swelling, Localised oedema, Oedema, Oedema peripheral, Periorbital oedema).

Reference: 1. XALKORI® Summary of Product Characteristics. MMMM 2015.

ADVERSE REACTIONS REPORTED WITH **XALKORI®**

- The most serious adverse reactions with XALKORI® are hepatotoxicity, interstitial lung disease (ILD)/pneumonitis, neutropenia and QTc interval prolongation.
- The most common adverse reactions (≥25%) with XALKORI® are vision disorder, nausea, diarrhoea, vomiting, oedema, constipation, elevated transaminases, decreased appetite, fatigue, dizziness and neuropathy.

MANAGEMENT OF ADVERSE REACTIONS WITH **XALKORI®**

HEPATATOTOXICITY

- Drug-induced hepatotoxicity with fatal outcome has occurred in less than 0.5% of patients with ALK-positive advanced NSCLC (N=1,669), treated with XALKORI® across clinical studies.[1]
- Concurrent elevations in ALT and/or AST ≥3 x ULN and total bilirubin ≥2 x ULN without significant elevations of alkaline phosphatase (≤2 × ULN) have been observed in less than 1% of patients in clinical trials.
- Increases to Grade 3 or 4 ALT or AST elevations were observed in 11% and 6% of patients, respectively.
- In PROFILE 1014, increases to Grade 3 or 4 ALT or AST elevations were observed in 15% and 8% of patients receiving crizotinib versus 2% and 1% of patients receiving chemotherapy. In PROFILE 1007, increases to Grade 3 or 4 ALT or AST elevations were observed in 18% and 9% of patients receiving crizotinib and 5% and <1% of patients receiving chemotherapy.
- Transaminase elevations generally occurred within the first 2 months of treatment. Grade 3 and 4 transaminase elevations were generally reversible upon dosing interruption. Across studies with crizotinib in patients with ALK-positive NSCLC (N=1,669), dose reductions associated with transaminase elevations occurred in 4% of patients, and 1% of patients required permanent discontinuation from treatment.
- XALKORI® should not be used in patients with severe hepatic impairment.

Transaminases (ALT, AST) and total bilirubin should be monitored once a week during the first 2 months of treatment, then once a month and as clinically indicated, with more frequent repeat testing for Grades 2, 3 or 4 elevation[1].

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.

Reference: 1. XALKORI® Summary of Product Characteristics. MMMM 2015.

MANAGEMENT OF ADVERSE REACTIONS WITH **XALKORI®**

Patients should be monitored for hepatotoxicity. Treatment with XALKORI® should be used with caution in patients with mild and moderate hepatic impairment. XALKORI® should not be used in patients with severe hepatic impairment.

It is important to counsel patients about the risk of hepatotoxicity and inform them of what symptoms and signs to be aware of and actions to take.

DOSE MODIFICATION ON DETECTION OF TRANSAMINASE ELEVATIONS[1]	
Grade 3 or 4 ALT or AST elevation with Grade ≤1 total bilirubin.	• Withhold until recovery to Grade ≤1 or baseline, then resume at 250 mg once daily and escalate to 200 mg twice daily if clinically tolerated.*
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.

*XALKORI® must be permanently discontinued in case of further Grade ≥3 recurrence.

ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Reference: 1. XALKORI® Summary of Product Characteristics. MMMM 2015.

MANAGEMENT OF ADVERSE REACTIONS WITH **XALKORI®**

INTERSTITIAL LUNG DISEASE (ILD)/PNEUMONITIS

- Severe, life-threatening, and/or fatal interstitial lung disease (ILD)/pneumonitis can occur in patients treated with XALKORI®. Across studies in patients with ALK-positive advanced NSCLC (N=1,669), 3% of patients treated with crizotinib had any grade all-causality ILD, including 1% of patients with Grade 3 or 4, and <1% of patients with fatal cases. These cases generally occurred within 3 months after the initiation of treatment. Other potential causes of ILD/pneumonitis should be excluded.
- Patients should be monitored for any pulmonary symptoms indicative of ILD/pneumonitis. XALKORI® treatment should be withheld if ILD/pneumonitis is suspected. Drug-induced ILD/pneumonitis should be considered in the differential diagnosis of patients with ILD-like conditions such as: pneumonitis, radiation pneumonitis, hypersensitivity pneumonitis, interstitial pneumonitis, pulmonary fibrosis, acute respiratory distress syndrome (ARDS), alveolitis, lung infiltration, pneumonia, pulmonary oedema, chronic obstructive pulmonary disease, pleural effusion, aspiration pneumonia, bronchitis, obliterative bronchiolitis, and bronchiectasis.
- XALKORI® treatment should be permanently discontinued in patients diagnosed with treatment-related ILD/pneumonitis.

DOSE MODIFICATION ON DETECTION OF PNEUMONITIS[1]	
Any Grade ILD/pneumonitis.*	• Withhold if ILD/pneumonitis is suspected, and permanently discontinue if treatment-related ILD/pneumonitis is diagnosed.

*XALKORI® must be permanently discontinued in case of further Grade ≥3 recurrence.

It is important to counsel patients about the risk of ILD/pneumonitis and inform them of what symptoms and signs to be aware of and actions to take.

Reference: 1. XALKORI® Summary of Product Characteristics. MMMM 2015.

MANAGEMENT OF ADVERSE REACTIONS WITH **XALKORI®**

QTc PROLONGATION

- QTc prolongation has been observed, which may lead to an increased risk for ventricular tachyarrhythmias (e.g., Torsade de Pointes) or sudden death.
- Across studies in patients with ALK-positive advanced NSCLC, QTcF ≥500 msec was recorded in 2.1% of 1,560 patients and a maximum increase from baseline in QTcF ≥60 msec was observed in 5.0% of 1,520 patients. Grade 3 or 4 all-causality electrocardiogram QT prolonged was reported in 1.5% out of 1,669 patients.

DOSE MODIFICATION ON DETECTION OF QTC PROLONGATION[1]	
Grade 3.	• Withhold until recovery to Grade ≤1, check and if necessary correct electrolytes, then resume at 200 mg twice daily.*
Grade 4.	• Permanently discontinue.

*XALKORI® must be permanently discontinued in case of further Grade ≥3 recurrence.

QTc = corrected QT interval.

Reference: 1. XALKORI® Summary of Product Characteristics. MMMM 2015.

MANAGEMENT OF ADVERSE REACTIONS WITH **XALKORI**®

The benefits and potential risks of XALKORI® should be considered before beginning therapy in patients with pre-existing bradycardia, who have a history of or predisposition for QTc prolongation, who are taking antiarrhythmics or other medicinal products that are known to prolong QT interval and in patients with relevant pre-existing cardiac disease, and/or electrolyte disturbances.

XALKORI® should be administered with caution in these patients and periodic monitoring of electrocardiograms (ECGs), electrolytes and renal function is required.

ECG and electrolytes (e.g., calcium, magnesium, potassium) should be obtained as close as possible prior to the first dose of XALKORI® and periodic monitoring with ECG and electrolytes is recommended, especially at the beginning of treatment in case of vomiting, diarrhoea, dehydration or impaired renal function. Correct electrolytes as necessary.

If QTc increases by greater than or equal to 60 msec from baseline but QTc is <500 msec, crizotinib should be withheld and cardiologist advice should be sought. If QTc increases to greater than or equal to 500 msec, cardiologist advice must be immediately sought.[1]

It is important to counsel patients about the risk of prolonged QTc and inform them of what symptoms to be aware of and actions to take.

QTc = corrected QT interval.

Reference: 1. XALKORI® Summary of Product Characteristics. MMMM 2015.

MANAGEMENT OF ADVERSE REACTIONS WITH **XALKORI®**

BRADYCARDIA

- Across studies with crizotinib in patients with ALK-positive advanced NSCLC (N=1,669), all-causality bradycardia was experienced by 12% of patients treated with crizotinib. Symptomatic bradycardia (e.g., syncope, dizziness, hypotension) can occur in patients receiving XALKORI®.

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.

Monitor heart rate and blood pressure regularly.

Dose modification is not required in cases of asymptomatic bradycardia. For management of patients who develop symptomatic bradycardia, see below.

It is important to counsel patients about the risk of bradycardia and inform them of what symptoms and signs to be aware of and actions to take.

DOSE MODIFICATION ON DETECTION OF BRADYCARDIA[1]	
Grade 2, 3 Bradycardia* Symptomatic, may be severe and medically significant, medical intervention indicated.	• Withhold until recovery to Grade ≤1 or to heart rate 60 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 60 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 60 or above.
Grade 4 Bradycardia*† 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 60 or above, with frequent monitoring.

*Heart rate less than 60 beats per minute (bpm). †Permanently discontinue for recurrence.

Reference: 1. XALKORI® Summary of Product Characteristics. MMMM 2015.

MANAGEMENT OF ADVERSE REACTIONS WITH **XALKORI**®

VISUAL EFFECTS

- Across studies in patients with ALK-positive advanced NSCLC (N=1,669), all-causality vision disorder, most commonly visual impairment, photopsia, vision blurred, and vitreous floaters, was experienced by 62% of patients treated with crizotinib. Ninety-five percent of these patients had events that were mild in severity. The onset of vision disorders generally was within the first week of crizotinib administration.
- A total of 0.4% of patients had temporary treatment discontinuation and 0.1% of patients had a dose reduction associated with vision disorder. There were no permanent treatment discontinuations associated with vision disorder for any of the 1,669 patients treated with crizotinib.

Ophthalmological evaluation (e.g., visual acuity, fundoscopy, and slit lamp examinations) should be considered if visual effects persist or worsen.[1]

Patients who experience visual effects should be advised to take special care when driving and using machines.[1]

Counsel patients about the risk of vision disorders and inform them of what symptoms to be aware of and the actions to take.

Reference: 1. XALKORI® Summary of Product Characteristics. MMMM 2015.

MANAGEMENT OF ADVERSE REACTIONS WITH **XALKORI®**

GASTROINTESTINAL EFFECTS INCLUDING GASTROINTESTINAL PERFORATION

- Gastrointestinal perforations were uncommonly reported. There were reports of fatal cases of gastrointestinal perforation during post-marketing use of XALKORI®.
- Nausea, diarrhoea, vomiting, and constipation were the most commonly reported all-causality gastrointestinal events. Median times to onset for nausea and vomiting were 4 days. Most of these events were mild to moderate in severity, and declined in frequency after 3 to 4 weeks. Supportive care should include the use of antiemetic medicinal products.
- 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.

Crizotinib 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 medications with a recognised risk of gastrointestinal perforation).

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

NERVOUS SYSTEM EFFECTS

- Across studies in patients with ALK-positive advanced NSCLC (N=1,669), all-causality neuropathy was experienced by 25% of patients treated with crizotinib.
- Dysgeusia was very commonly reported in these studies, and was primarily Grade 1 in severity.

Reference: 1. XALKORI® Summary of Product Characteristics. MMMM 2015.

MANAGEMENT OF ADVERSE REACTIONS WITH **XALKORI**®

RENAL CYSTS

- Across studies in patients with ALK-positive advanced NSCLC (N=1,669), all-causality complex renal cysts were experienced by 3% of patients treated with crizotinib.
- 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.

Reference: 1. XALKORI® Summary of Product Characteristics. MMMM 2015.

MANAGEMENT OF ADVERSE REACTIONS WITH **XALKORI®**

NEUTROPENIA AND LEUKOPENIA

- Across studies in patients with ALK-positive advanced NSCLC (N=1,669) Grade 3 or 4 neutropenia was observed in 12% of patients treated with crizotinib. Median time to onset of any grade neutropenia was 87 days. Neutropenia was associated with dose reduction or permanent treatment discontinuation for 4% and <1% of patients, respectively. Less than 0.5% of patients experienced febrile neutropenia in clinical studies with crizotinib.
- Across studies in patients with ALK-positive advanced NSCLC (N=1,669), Grade 3 or Grade 4 leukopenia was observed in 3% of patients. Median time to onset of any grade leukopenia was 85 days. Leukopenia was associated with a dose reduction for <0.5% of patients, and no patients permanently discontinued crizotinib treatment associated with leukopenia.
- In clinical studies of crizotinib in patients with ALK-positive advanced NSCLC, shifts to Grade 3 or 4 decreases in leukocytes and neutrophils were observed at frequencies of 4% and 14%, 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.

DOSE MODIFICATION ON DETECTION OF HAEMATOLOGIC TOXICITIES*[1]	
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.†

*Except lymphopenia (unless associated with clinical events, e.g., opportunistic infections).
†In case of recurrence, withhold until recovery to Grade ≤2, then resume at 250 mg taken orally once daily. Permanently discontinue in case of further Grade 4 recurrence.

Reference: 1. XALKORI® Summary of Product Characteristics. MMMM 2015.

ADMINISTRATION OF **XALKORI®** IN PATIENTS WITH SEVERE RENAL IMPAIRMENT

- XALKORI® plasma concentrations may be increased in patients with severe renal impairment (CLcr <30 mL/min) not requiring peritoneal dialysis or haemodialysis.[1]

XALKORI® starting 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.[1]

Reference: 1. XALKORI® Summary of Product Characteristics. MMMM 2015.

CO-ADMINISTRATION OF **XALKORI®** WITH OTHER MEDICATIONS

AGENTS THAT MAY INCREASE XALKORI® PLASMA CONCENTRATIONS

- Co-administration of XALKORI® with strong CYP3A inhibitors may increase XALKORI® plasma concentrations.[1]

Avoid concomitant use of strong CYP3A inhibitors including certain protease inhibitors (e.g., atazanavir, indinavir, nelfinavir, ritonavir, and saquinavir), certain azole antifungals (e.g., itraconazole, ketoconazole, and voriconazole) and certain macrolides (e.g., clarithromycin, telithromycin, and troleandomycin).[1]

Avoid consumption of grapefruit or grapefruit juice.[1]

AGENTS THAT MAY DECREASE XALKORI® PLASMA CONCENTRATIONS

- Co-administration of XALKORI® with strong CYP3A inducers may decrease XALKORI® plasma concentrations.[1]

Avoid concurrent use of strong CYP3A inducers, including but not limited to, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, and St. John's wort.[1]

CYP3A = cytochrome P4503A.

Reference: 1. XALKORI® Summary of Product Characteristics. MMMM 2015.

CO-ADMINISTRATION OF **XALKORI®** WITH OTHER MEDICATIONS

AGENTS WHOSE PLASMA CONCENTRATIONS MAY BE ALTERED BY **XALKORI®**

- XALKORI® is a moderate inhibitor of CYP3A.[1]

Co-administration of XALKORI® with CYP3A substrates with narrow therapeutic indices, including but not limited to alfentanil, cisapride, cyclosporine, ergot derivatives, fentanyl, pimozide, quinidine, sirolimus and tacrolimus, should be avoided.[1]

- XALKORI® is an inhibitor of CYP2B6.*[1]

XALKORI® may have the potential to increase plasma concentrations of co-administered drugs that are metabolised by CYP2B6 (e.g., bupropion, efavirenz).

- XALKORI® may induce PXR- and CAR-regulated enzymes (e.g., CYP3A4, CYP2B6, CYP2C8, CYP2C9, UGT1A1).*[1]

Exercise caution in administering XALKORI® in combination with medicinal products that are metabolised predominantly by these enzymes – the effectiveness of concomitant administration of oral contraceptives may be reduced.

- XALKORI® may be a P-gp inhibitor at therapeutic concentrations.*[1]

Exercise caution in administering XALKORI®, as it may have the potential to increase plasma concentrations of co-administered medicinal products that are substrates of P-gp (e.g., digoxin, dabigatran, colchicine, pravastatin).

* *In vitro* data.

CYP3A = cytochrome P4503A; P-gp = permeability glycoprotein; PXR = pregnane X receptor; CAR = constitutive androstane receptor.

Reference: 1. XALKORI® Summary of Product Characteristics. MMMM 2015.

CO-ADMINISTRATION OF **XALKORI®** WITH OTHER MEDICATIONS

- XALKORI® is a weak inhibitor of UGT1A1 and UGT2B7.*[1]

XALKORI® may have the potential to increase plasma concentrations of co-administered drugs that are metabolised predominantly by UGT1A1 (e.g., raltegravir, irinotecan) or UGT2B7 (e.g., morphine, naloxone).

- XALKORI® is an inhibitor of OCT1 and OCT2.*[1]

XALKORI® may have the potential to increase plasma concentrations of co-administered drugs that are substrates of OCT1 or OCT2 (e.g., metformin, procainamide).

**In vitro* data.

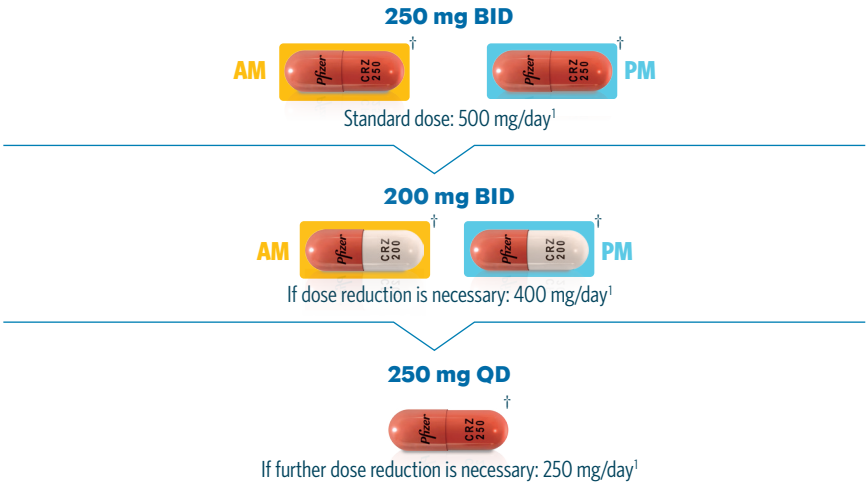
Reference: 1. XALKORI® Summary of Product Characteristics. MMMM 2015.

DOSE MODIFICATION GUIDANCE

DOSE ADJUSTMENTS

- Dosing interruption and/or dose reduction may be required based on individual safety and tolerability.
- Please refer to the Summary of Product Characteristics for dose adjustment guidelines for haematologic and non-haematologic toxicities.[1]

RECOMMENDED POSOLOGY[1]



†Capsule not shown in actual size.

Dose reduction may be required based on individual safety and tolerability[1]

- Please refer to the Summary of Product Characteristics for further guidance on dosing interruptions and dose reductions.
  - In 1,669 patients treated with crizotinib with ALK-positive advanced NSCLC across clinical studies, the most frequent adverse reactions (≥3%, all-causality frequency) associated with dosing interruptions were neutropenia, (11 %), elevated transaminases, (7%), vomiting, (5%), and nausea, (4%). The most frequent adverse reactions (≥3%, all-causality frequency) associated with dose reductions were elevated transaminases, (4%), and neutropenia, (4%).

BID = twice daily; QD = once daily.

Reference: 1. XALKORI® Summary of Product Characteristics. MMMM 2015.

XALKORI®
PRESCRIBING INFORMATION

XALKORI® ▼ Prescribing Information:
Please refer to the Summary of Product Characteristics (SmPC) before prescribing XALKORI 200 mg or 250 mg hard capsules.
Presentation: Hard capsules containing 200 mg or 250 mg crizotinib. **Indications:** Treatment of adults with previously treated anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC). **Dosage:** Therapy should be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products. An accurate and validated ALK assay is necessary for the selection of patients for treatment with XALKORI. ALK-positive NSCLC status should be established prior to initiation of XALKORI therapy. Assessment should be performed by laboratories with demonstrated proficiency in the specific technology being utilised. The recommended dose of XALKORI is 250 mg taken orally (twice daily) with or without food, continuously. Dosing interruption and/or dose reduction may be required based on individual safety and tolerability. If dose reduction is necessary, then the dose of XALKORI should be reduced to 200 mg taken twice daily. If further dose reduction is necessary, then the dose should be modified to 250 mg taken once daily based on individual safety and tolerability. For dose reduction guidelines for haematologic and non-haematologic toxicities, refer to SmPC section 4.2. Treatment should be used with caution in patients with mild and moderate hepatic impairment and contraindicated in patients with severe hepatic impairment. No starting dose adjustment is recommended for patients with mild ($60 \leq$ creatinine clearance [CLcr] <90 mL/min) or moderate ($30 \leq$ CLcr < 60 mL/min) renal impairment. Crizotinib plasma concentrations may be increased in patients with severe renal impairment (CLcr <30 mL/min). Crizotinib dose should be adjusted to 250 mg once daily in patients with severe renal impairment, not requiring peritoneal dialysis or haemodialysis, and may be increased to 200 mg twice daily based on individual safety and tolerability, after at least 4 weeks of treatment (refer to SmPC section 4.2). The safety and efficacy of XALKORI in paediatric patients has not been established. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Severe hepatic impairment. **Warnings and Precautions:** Drug-induced hepatotoxicity with fatal outcome has been reported. Monitor liver function tests including ALT, AST, and total bilirubin once a week during the first 2 months of treatment then once a month and as clinically indicated with more frequent testing for Grades 2, 3 or 4 elevations. Severe, life-threatening, and/or fatal interstitial lung disease (ILD)/pneumonitis has been reported. Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis. Withhold XALKORI treatment if ILD/pneumonitis is suspected. Drug-induced ILD/pneumonitis should be considered in the differential diagnosis of patients with ILD-like conditions (e.g. pulmonary oedema, pneumonitis etc). Xalkori should be permanently discontinued in patients diagnosed with treatment-related ILD/pneumonitis. QTc prolongation, which may lead to an increased risk for ventricular tachyarrhythmias (e.g., Torsade de Pointes) or sudden death, has been observed in clinical studies. The benefits and potential risks should be considered before beginning crizotinib in patients with pre-existing bradycardia, who have a history of or predisposition to QTc prolongation, who are taking antiarrhythmics or other medicinal products that are known to prolong QT interval and in patients with relevant preexisting cardiac disease and/or electrolyte disturbances. XALKORI should be administered with caution in these patients and periodic monitoring of electrocardiograms (ECG), electrolytes and renal function is required. ECG and electrolytes should be obtained as close as possible prior to the first dose and periodic monitoring is recommended, especially in case of vomiting, diarrhoea, dehydration or impaired renal function. Correct electrolytes as necessary. If QTc increases by ≥60 msec from baseline but QTc is < 500 msec, crizotinib should be withheld and cardiologist advice should be sought. If QTc increases to ≥500 msec, cardiologist advice must be immediately sought (see SmPC sections 4.2, 4.8 and 5.2). Treatment-emergent all-causality bradycardia was reported in clinical studies in 5 to 10% of patients treated with crizotinib. Symptomatic bradycardia can occur in patients receiving XALKORI. The full effect of crizotinib on reduction of heart 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. Monitor heart rate and blood pressure regularly. Dose modification is not required in cases of asymptomatic bradycardia. For management of patients who develop symptomatic bradycardia, see SmPC sections 4.2 and 4.8. In clinical trials with crizotinib Grade 3 or 4 neutropenia has been very commonly (6%–13%) reported. Grade 3 or 4 leukopenia has been commonly (2%) reported and less than 1% of patients experienced febrile neutropenia. Complete blood 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 clinical studies with crizotinib, events of gastrointestinal perforations were reported with reports of fatal cases during post-marketing use. (see SmPC section 4.8). Crizotinib 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 medications with a recognised risk of gastrointestinal perforation). Crizotinib should be discontinued in patients who develop gastrointestinal perforation. Patients should be informed of the first signs of gastrointestinal perforations and advised to seek emergency medical attention in case of occurrence. Vision disorder was experienced in clinical studies. Ophthalmological evaluation should be considered if vision disorder persists or worsens in severity. Concomitant use of crizotinib with strong CYP3A4 inhibitors/inducers, and CYP3A4 substrates with narrow therapeutic indices should be avoided. Avoid using crizotinib in combination with other bradycardic agents, medicinal products that are known to prolong QT interval and/or antiarrhythmics. **Drug Interactions:** *In vitro* studies indicated that crizotinib is an inhibitor of CYP2B6. Therefore, crizotinib may have the potential to increase plasma concentrations of coadministered drugs that are metabolized by CYP2B6 (e.g., bupropion, efavirenz). *In vitro* studies indicated that crizotinib may induce pregnane X receptor (PXR)- and constitutive androstane receptor (CAR)-regulated enzymes (e.g. CYP3A4, CYP2B6, CYP2C8, CYP2C9, UGT1A1). However, there was no observed induction *in vivo* when crizotinib was coadministered with the CYP3A probe substrate midazolam. Caution should be exercised in administering crizotinib in combination with medicinal products that are predominantly metabolized by these enzymes. Effectiveness of concomitantly administered oral contraceptives may be reduced. *In vitro* studies indicated that crizotinib is a weak inhibitor of UGT1A1 and UGT2B7. Therefore, crizotinib may have the potential to increase plasma concentrations of coadministered drugs that are metabolized predominantly by UGT1A1 (e.g. raltegravir, irinotecan) or UGT2B7 (e.g., morphine, naloxone). Based on an *in vitro* study, crizotinib is predicted to inhibit intestinal P-gp.Therefore, administration of crizotinib with medicinal products that are substrates of P-gp (e.g. digoxin, dabigatran, colchicines, pravasatatin) may increase their therapeutic effect and adverse reactions. Crizotinib is an inhibitor of OCT1 and OCT2 *in vitro*. Therefore, crizotinib may have the potential to increase plasma concentrations of coadministered drugs that are substrates of OCT1 or OCT2 (metformin, procainamide). Prolonged QT interval has been observed with crizotinib. The concomitant use of crizotinib with medicinal products known to prolong QT interval or able to induce Torsades de pointes (e.g., class IA [quinidine, disopyramide] or class III [e.g., amiodarone, sotalol, dofetilide, ibutilide], methadone, asapride, moxifloxacine, antipsychotics, etc.) should be carefully considered. A monitoring of the QT interval should be made in case of combinations of such medicinal products. Use with caution due to the risk of excessive bradycardia when used in combination with other bradycardic agents (e.g. nondihydropyridine calcium channel blockers such as verapamil and diltiazem, beta-blockers, clonidine, guanfacine, digoxin, mefloquine, anticholinesterases, pilocarpine). **Pregnancy & Lactation:** Not recommended in pregnancy or whilst breast-feeding. Adequate contraceptive methods should be used during therapy, and for at least 90 days after completing therapy. Crizotinib may impair fertility and both men and women should seek advice on fertility preservation before treatment. **Driving and operating machinery:** Caution should be exercised when driving or operating machines as patients may experience symptomatic bradycardia (e.g., syncope, dizziness, hypotension), vision disorder, or fatigue while taking XALKORI. **Side Effects:** The most serious adverse reactions in patients with ALK-positive advanced NSCLC are hepatotoxicity, ILD/pneumonitis, neutropenia and QT interval prolongation. Very common adverse events are neutropenia, anaemia, decreased appetite, neuropathy, dysgeusia, vision disorder, dizziness, diarrhoea, vomiting, nausea, constipation, elevated transaminases, oedema, fatigue. Commonly reported adverse events are leukopenia, hypophosphataemia, electrocardiogram QT prolonged, bradycardia, syncope, interstitial lung disease, dyspepsia, elevated blood alkaline phosphatase, rash, renal cyst. Refer to SmPC for further information on side effects. **Legal Category:** POM. **Marketing authorisation holder:** Pfizer Ltd, Ramsgate Road, Sandwich, Kent, CT13 9NJ, UK. **Package quantities, Marketing Authorisation numbers and basic NHS price:** XALKORI 200mg, 60 capsules, EU/1/12/793/001 £4689; XALKORI 250mg, 60 capsules, EU/1/12/793/003 £4689. **Further information is available on request from:** Medical Information at Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey, KT20 7NS, UK. Tel: +44 (0) 1304 616161.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Pfizer Medical Information on 01304 616161.

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 of the SmPC for how to report adverse reactions.

Pfizer Oncology

XALKORI® CRIZOTINIB