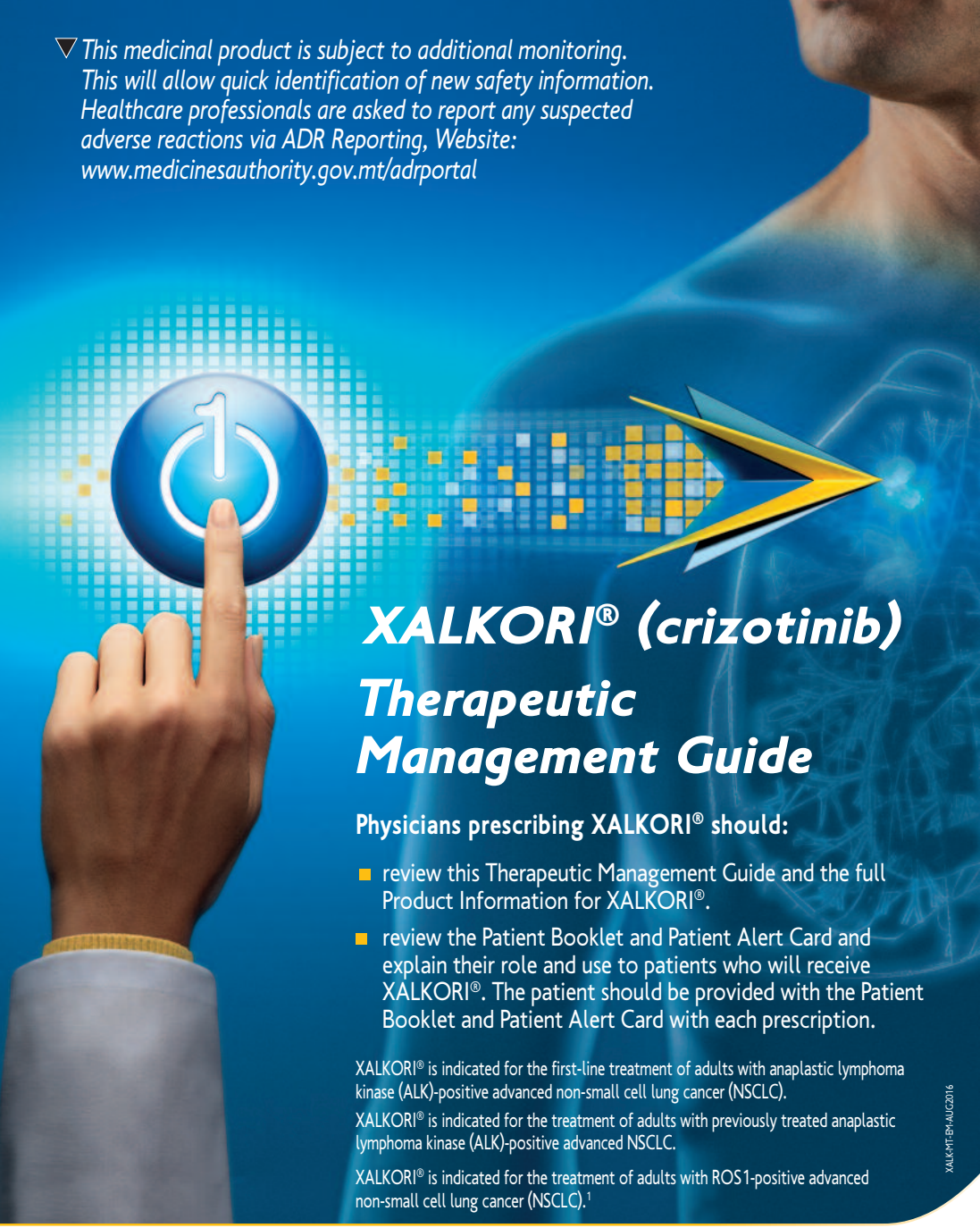
▼ *This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions via ADR Reporting, Website: www.medicinesauthority.gov.mt/adrportal*



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.

XALKORI® is indicated for the treatment of adults with ROS1-positive advanced non-small cell lung cancer (NSCLC).[1]

XALK-MT-BY-AUG2016

Reference: 1. XALKORI® Summary of Product Characteristics 2016 is enclosed with this package.

Pfizer Oncology

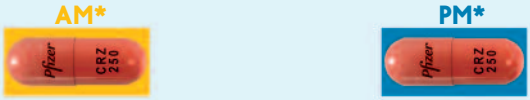
Pfizer Hellas S.A. 243 Messoghion Ave. N.Psychiko, Athens GR-15451, Greece
Local Representative: V.J. Salomone Pharma Ltd., Upper Cross Road, Marsa MRS 1542, Malta

XALKORI® CRIZOTINIB

XALKORI® DOSING

EITHER ALK-POSITIVE OR ROS1-POSITIVE NSCLC STATUS SHOULD BE ESTABLISHED PRIOR TO INITIATION OF XALKORI® THERAPY. AN ACCURATE AND VALIDATED ASSAY FOR EITHER ALK OR ROS1 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



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 2016.

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) AND IN 53 PATIENTS WITH ROS1-POSITIVE ADVANCED NSCLC WHO PARTICIPATED IN SINGLE-ARM STUDY (PROFILE 1001), FOR A TOTAL OF 1,722 PATIENTS.

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] (63%)		
Cardiac disorders	Dizziness[f] (26%) Bradycardia[g] (13%)	Cardiac failure[h] (1%) Electrocardiogram QT prolonged (4%) Syncope (3%)	
Respiratory, thoracic and mediastinal disorders		Interstitial Lung Disease[i] (3%)	
Gastrointestinal disorders	Vomiting (51%) Diarrhoea (54%) Nausea (57%) Constipation (43%) Abdominal pain[j] (21%)	Dyspepsia (8%) Oesophagitis[k] (2%)	Gastrointestinal perforation[l] (<1%)
Hepatobiliary disorders	Elevated transaminases[m] (32%)	Blood alkaline phosphatase increased (7%)	Hepatic failure (<1%)
Skin and subcutaneous tissue disorders	Rash (13%)		
Renal and urinary disorders		Renal cyst[n] (3%) Blood creatinine increased[o] (8%)	Acute renal failure (<1%) Renal failure (<1%)
General disorders and administration site conditions	Oedema[p] (47%) Fatigue (30%)		
Investigations		Blood testosterone decreased[q] (2%)	

Event terms that represent the same medical concept or condition were grouped together and reported as a single adverse reaction in the above table. Terms actually reported in the study 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, 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 impairment, Visual perseveration, Vitreous floaters). [f]Dizziness (Balance disorder, Dizziness, Dizziness postural, Presyncope). [g]Bradycardia (Bradycardia, Heart rate decreased, 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 crizotinib 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 (Alanine aminotransferase increased, Aspartate aminotransferase increased, Gamma-glutamyltransferase increased, Hepatic enzyme increased, Hepatic function abnormal, Liver function test abnormal, Transaminases increased). [n]Renal Cyst (Renal abscess, Renal cyst, Renal cyst haemorrhage, Renal cyst infection, [o]Blood creatinine increased (blood creatinine increased, creatinine renal clearance decreased). [p]Oedema (Face oedema, Generalised oedema, Local swelling, Localised oedema, Oedema, Oedema peripheral, Periorbital oedema). [q]Blood testosterone decreased (Blood testosterone decreased, Hypogonadism, Secondary hypogonadism).

Reference: 1. XALKORI® Summary of Product Characteristics 2016.

ADVERSE REACTIONS REPORTED WITH **XALKORI**®

- The most serious adverse reactions in 1,722 patients with either ALK-positive or ROS1 positive advanced NSCLC were hepatotoxicity, interstitial lung disease (ILD)/pneumonitis, neutropenia and QT interval prolongation.
- 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, fatigue, decreased appetite, dizziness and neuropathy.

Reference: 1. XALKORI® Summary of Product Characteristics 2016.

MANAGEMENT OF ADVERSE REACTIONS WITH **XALKORI®**

HEPATATOTOXICITY

- Drug-induced hepatotoxicity with fatal outcome has occurred in 0.1% of patients with either ALK-positive or ROS1-positive advanced NSCLC (N=1,722), 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% 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 either ALK-positive or ROS1-positive advanced NSCLC (N=1722), 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 2016.

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 2016.

MANAGEMENT OF ADVERSE REACTIONS WITH **XALKORI®**

INTERSTITIAL LUNG DISEASE/PNEUMONITIS

- Severe, life-threatening, and/or fatal interstitial lung disease (ILD)/pneumonitis can occur in patients treated with XALKORI®. Across studies in patients with either ALK-positive or ROS1-positive advanced NSCLC (N=1722), 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. According to independent review committee (IRC) assessment, of patients with ALK-positive advanced NSCLC (N=1669), 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. 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 interstitial lung disease/pneumonitis.	• Withhold if interstitial lung disease/pneumonitis is suspected, and permanently discontinue if treatment-related ILD/pneumonitis is diagnosed.

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

Reference: 1. XALKORI® Summary of Product Characteristics 2016.

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 either ALK-positive or ROS1-positive advanced NSCLC, QTcF ≥500 msec was recorded in 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 5.0% of 1585 patients with a baseline and at least 1 postbaseline ECG assessment. Grade 3 or 4 all-causality Electrocardiogram QT prolonged was reported in 1.6% out of 1722 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 2016.

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 (ECG), 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 ECGs 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 2016.

MANAGEMENT OF ADVERSE REACTIONS WITH **XALKORI®**

BRADYCARDIA

- Across studies with crizotinib in patients with either ALK-positive or ROS1-positive advanced NSCLC (N=1722), all-causality bradycardia was experienced by 13% 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 2016.

MANAGEMENT OF ADVERSE REACTIONS WITH **XALKORI®**

CARDIAC FAILURE

- In clinical studies with crizotinib and during post marketing surveillance, severe, life-threatening, or fatal adverse reactions of cardiac failure were reported.

Patients with or without pre-existing cardiac disorders, receiving crizotinib, 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[1].

VISUAL EFFECTS

- In clinical studies with crizotinib in patients with either ALK-positive or ROS1-positive advanced NSCLC (N=1722), Grade 4 visual field defect with vision loss has been reported in 0.2% patients. Optic atrophy and optic nerve disorder have been reported as potential causes of vision loss.
- All-causality vision disorder, most commonly visual impairment, photopsia, vision blurred, and vitreous floaters, was experienced by 63% of 1722 patients treated with crizotinib. Of the 1084 patients who experienced vision disorder, 95% 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 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 1722 patients treated with crizotinib.

In patients with new onset of severe visual loss (best corrected visual acuity less than 6/60 in one or both eyes), XALKORI® treatment should be discontinued. Ophthalmological evaluation consisting of best corrected visual acuity, retinal photographs, visual fields, optical coherence tomography (OCT) and other evaluations as appropriate for new onset of severe visual loss, should be performed. There is insufficient information to characterize the risks of resumption of XALKORI® in patients with a severe visual loss. A decision to resume XALKORI® should consider the potential benefit to the patient.

Ophthalmological evaluation is recommended 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.

DOSE MODIFICATION ON DETECTION OF SEVERE VISUAL LOSS[1]	
Grade 4 Ocular Disorder (Visual Loss)	• Discontinue during evaluation of severe vision loss

Reference: 1. XALKORI® Summary of Product Characteristics 2016.

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. 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. Supportive care should include the use of antiemetic medicinal products.
- 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 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 perforations and be advised to consult rapidly in case of occurrence.

Reference: 1. XALKORI® Summary of Product Characteristics 2016.

MANAGEMENT OF ADVERSE REACTIONS WITH **XALKORI**®

RENAL EFFECTS

- Blood creatinine increase and creatinine clearance decreased were observed in patients in clinical studies with crizotinib. Renal failure and acute renal failure were reported in patients treated with crizotinib in clinical trials and during post marketing. Cases with fatal outcome, cases requiring hemodialysis and cases of grade 4 hyperkalemia were also observed.

Monitoring of patients for renal function at baseline and during therapy with crizotinibis recommended, with particular attention to those who have risk factors or previous history of renal impairment[1].

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.

RENAL CYST

- Across studies in patients with either ALK-positive or ROS1-positive advanced NSCLC (N=1722), 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 2016.

MANAGEMENT OF ADVERSE REACTIONS WITH **XALKORI®**

NEUTROPENIA AND LEUKOPENIA

- Across studies in patients with either ALK-positive or ROS1-positive advanced NSCLC (N=1722) Grade 3 or 4 neutropenia was observed in 212 (12%) patients treated with crizotinib. Median time to onset of any grade neutropenia was **89** days. Neutropenia was associated with dose reduction or permanent treatment discontinuation for 3% and <1% of patients, respectively. Less than 0.5% of patients experienced febrile neutropenia in clinical studies with crizotinib.
- Across studies in patients with either ALK-positive or ROS1-positive advanced NSCLC (N=1722), Grade 3 or Grade 4 leukopenia was observed in 48 (3%) patients treated with crizotinib. 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 either ALK-positive or ROS1-positive advanced NSCLC, shifts to Grade 3 or 4 decreases in leukocytes and neutrophils were observed at frequencies of 4% and 13%, 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 2016.

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 2016.

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

- Coadministration of repeated doses of crizotinib (250 mg twice daily) with repeated doses of rifampicin (600 mg once daily), a strong CYP3A4 inducer, resulted in 84% and 79% decreases in crizotinib steady state AUC_{tau} and C_{max}, respectively, compared to when crizotinib was given alone.[1]

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

The effect of a moderate inducer including but not limited to efavirenz or rifabutin on crizotinib concentrations (i.e. decrease in crizotinib exposure at steady-state) is not clearly established therefore, their combination with crizotinib should be also avoided.[1]

CYP3A = cytochrome P4503A.

Reference: 1. XALKORI® Summary of Product Characteristics 2016.

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 2016.

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).

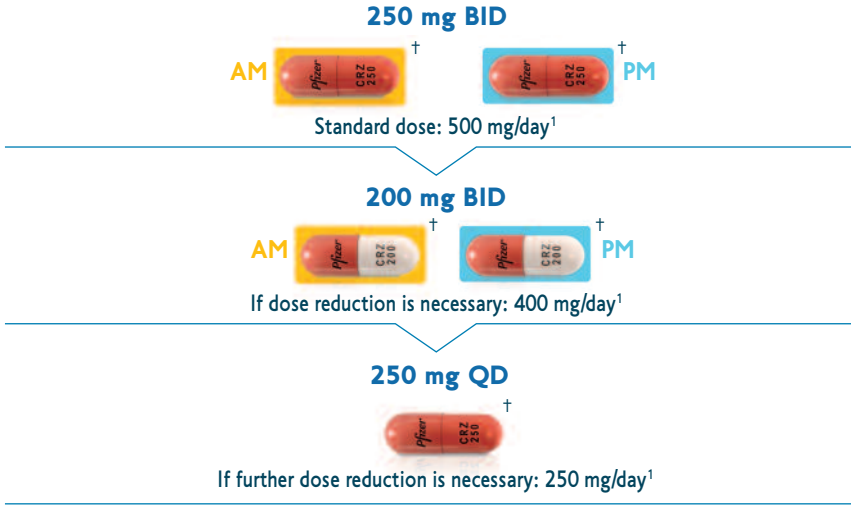
**In vitro* data.

Reference: 1. XALKORI® Summary of Product Characteristics 2016.

DOSE MODIFICATION GUIDANCE

- 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 1722 patients treated with crizotinib with either ALK-positive or ROS1-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 (3%).

BID = twice daily; QD = once daily.

Reference: 1. XALKORI® Summary of Product Characteristics 2016.

XALKORI®

Reporting of suspected adverse reactions

Suspected adverse reactions and medication errors should be reported.
Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal
and sent by post or email to:
P: ADR Reporting/ Sir Temi Zammit Buildings, Malta Life Sciences Park,
San Gwann SGN 3000, Malta
E: postlicensing.medicinesauthority@gov.mt

Other Contact Information

For any suspected adverse reactions you may also report such events promptly to Pfizer at Pfizer Hellas S.A. 243 Messoghion Ave. N.Psychiko, Athens GR-15451, Greece.
Pfizer Hellas Pharmacovigilance Department contact details:
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For more information, please contact Pfizer Hellas S.A. Medical Information at
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