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

XALKORI®

Therapeutic management guide

▼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,The Medicines Authority, Post-Licensing Directorate,203 Level 3, Rue D'Argens, GŻR-1368 Gżira
Website: www.medicinesauthority.gov.mt, e-mail: postlicensing.medicinesauthority@gov.mt

XALK-MT EM-JUL2013

* Crizotinib was granted 'conditional approval' by the European Medicines Agency (EMA). Confirmatory randomised Phase III studies are underway, and will be submitted to the EMA once available.

Reference: 1. XALKORI® Summary of Product Characteristics 2012 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

NEW XALKORI® CRIZOTINIB

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 

* **250 mg**

PM 

* **250 mg**

*Capsules not shown in actual size.

ALK, anaplastic lymphoma kinase

References: 1. XALKORI® Summary of Product Characteristics 2013.

Most common adverse reactions with XALKORI® were mild to moderate

ADVERSE REACTIONS IN XALKORI® REGISTRATION STUDIES[1]

ADVERSE REACTIONS REPORTED[a] N (%)	FREQUENCY[b]	(N= 386)	
		ALL GRADES	GRADE 3/4
Blood and lymphatic system disorders			
Neutropaenia	Very common	39 (10)	26 (7)
Leukopaenia	Common	17 (4)	2 (<1)
Lymphopaenia	Common	9 (2)	8 (2)
Anaemia	Common	6 (2)	1 (<1)
Metabolism and nutrition disorders			
Decreased Appetite	Very Common	73 (19)	0 (0)
Hypophosphataemia	Common	10 (3)	6 (2)
Nervous system disorders			
Neuropathy[c]	Very Common	44 (11)	2 (<1)
Dizziness	Very Common	59 (15)	0 (0)
Dysgeusia	Very Common	51 (13)	0 (0)
Eye disorders			
Vision Disorder[c]	Very Common	225 (58)	1 (<1)
Cardiac disorders			
Bradycardia[c]	Common	14 (4)	0 (0)
Respiratory, thoracic and mediastinal disorders			
Pneumonitis	Common	4 (1)	4 (1)[d]
Gastrointestinal disorders			
Vomiting	Very Common	157 (41)	3 (<1)
Nausea	Very Common	208 (54)	2 (<1)
Diarrhoea	Very Common	160 (42)	2 (<1)
Constipation	Very Common	111 (29)	0 (0)
Oesophageal-related disorder[c]	Common	24 (6)	0 (0)
Dyspepsia	Common	19 (5)	0 (0)
Skin and subcutaneous tissue disorders			
Rash	Common	35 (9)	0 (0)
Renal and urinary disorders			
Renal cyst[e]	Uncommon	2 (<1)	1 (<1)
General disorders and administration site conditions			
Fatigue[c]	Very Common	86 (22)	6 (2)
Oedema[c]	Very Common	104 (27)	0 (0)
Investigations			
Alanine aminotransferase increased	Very Common	53 (14)	20 (5)
Electrocardiogram QT prolonged	Common	4 (1)	2 (<1)
Aspartate aminotransferase increased	Common	38 (10)	7 (2)
Blood alkaline phosphatase increased	Common	9 (2)	0 (0)

[a] PROFILE 1001 used NCI CTCAE version 3.0. PROFILE 1005 used NCI CTCAE version 4.0.
[b] Based on the highest frequency between studies.
[c] Includes cases reported within the clustered terms: oedema (oedema, oedema peripheral), oesophageal-related disorder (gastroesophageal reflux disease, odynophagia, oesophageal pain, oesophageal ulcer, oesophagitis, reflux oesophagitis, dysphagia, epigastric discomfort), neuropathy (neuralgia, neuropathy peripheral, paraesthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, sensory disturbance), vision disorder (diplopia, photopsia, vision blurred, visual impairment, vitreous floaters), bradycardia (bradycardia, sinus bradycardia), and fatigue (asthenia, fatigue).
[d] Includes one Grade 5 event.
[e] Includes complex renal cysts.
CTCAE, CommonTerminology Criteria for Adverse Events; NCI, National Cancer Institute.

- Visual events were mostly Grade[1]
- Ophthalmological evaluation should be considered if vision disorder persists or worsens in severity[1]
- Drug-induced hepatotoxicity with fatal outcome has occurred during XALKORI® treatment, in less than 1% of patients in clinical trials[1]
- XALKORI® has been associated with severe, life-threatening or fatal treatment-related pneumonitis in 1% of patients across PROFILE 1001 and PROFILE 1005. All of these cases occurred within 2 months of treatment initiation[1]
- Please refer to the XALKORI® Summary of Product Characteristics for further information

NEW XALKORI® CRIZOTINIB

References: 1. XALKORI® Summary of Product Characteristics 2013.

Management of adverse reactions with XALKORI®

Hepatotoxicity

- Drug-induced hepatotoxicity with fatal outcome has occurred in ‹ 1 % of patients receiving XALKORI® in clinical studies[1]
- Concurrent elevations in ALT greater › 3 x ULN and total bilirubin › 2 x ULN without elevated alkaline phosphatase have been observed in ‹ 1 % patients in clinical trials.
- Increases to Grade 3 or 4 ALT elevation were observed in 6 % of patients in PROFILE 1001 and 8 % of patients in PROFILE 1005. Grades 3 and 4 elevations were generally asymptomatic and reversible upon dosing interruption. Patients usually resumed treatment at a lower dose without recurrence.
- Transaminase elevations generally occurred within the first 2 months of treatment. XALKORI® should not be used in patients with severe hepatic impairment

Liver function tests including, ALT, AST and total bilirubin, should be monitored twice a month 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]

DOSE MODIFICATION ON DE TECTION 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 200 mg twice daily*
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

* In case of recurrence, withhold until recovery to Grade ≤1, then resume at 250 mg taken once daily. Permanently discontinue in case of further Grade 3 or 4 recurrence.

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

References: 1. XALKORI® Summary of Product Characteristics 2013.

Management of adverse reactions with XALKORI®

Pneumonitis

- XALKORI® has been associated with severe, life-threatening, or fatal treatment-related pneumonitis in 1% of patients in clinical studies[1]. All of these cases occurred within 2 months after the initiation of treatment.

Patients with pulmonary symptoms indicative of pneumonitis should be monitored[1]

DOSE MODIFICATION ON DETECTION OF PNEUMONITIS	
Any Grade*	➤ Permanently discontinue if treatment-related pneumonitis is diagnosed*

* Treatment-related: not attributable to non-small cell lung cancer progression, other pulmonary disease, infection, or radiation effect. Withhold if pneumonitis is suspected until other causes of pneumonitis have been excluded. Permanently discontinue if treatment-related pneumonitis is diagnosed.

References: 1. XALKORI® Summary of Product Characteristics 2013.

Management of adverse reactions with XALKORI®

QT interval prolongation

- QTc prolongation has been observed, which may lead to an increased risk for ventricular tachyarrhythmias (e.g. Torsade de Pointes) or sudden death.
- The risk of QTc prolongation may be increased in patients concomitantly taking antiarrhythmics and in patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances (e.g. secondary to diarrhoea or vomiting).

DOSE MODIFICATION ON DE TECTION OF QTC PROLONGATION[1]	
Grade 3	➤ Withhold until recovery to Grade ≤ 1, then resume at 200 mg twice daily*
Grade 4	➤ Permanently discontinue

* 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 or 4 recurrence.

XALKORI® should be administered with caution to patients who have a history of or predisposition for QTc prolongation, or who are taking medicinal products that are known to prolong the QT interval[1]

When using XALKORI® in these patients, periodic monitoring with electrocardiograms and electrolytes should be considered[1]

QTc, Q-T corrected.

References: 1. XALKORI® Summary of Product Characteristics 2013.

Management of adverse reactions with XALKORI®

Visual effects

- Vision disorder including diplopia, photopsia, vision blurred, visual impairment, and vitreous floaters was experienced.
- Occurred in approximately 60% of patients included in the clinical trials, were mostly Grade 1 or 2 in severity and did not lead to permanent discontinuation.
- Were transient (lasting up to 60 seconds) in most patients.

Ophthalmological evaluation should be considered if visual effects persist or worsen in severity[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 and signs to be aware of and the actions to take.

References: 1. XALKORI® Summary of Product Characteristics 2013.

NEW XALKORI® CRIZOTINIB

Management of adverse reactions with XALKORI®

Haematologic laboratory abnormalities

- Grade 3 or 4 haematologic abnormalities were recorded in some patients receiving XALKORI® in registration studies[1]

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[1]

DOSE MODIFICATION ON DE TECTION OF HAEM ATOLOGIC ABNORMALITIES[†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 ➤ In case of recurrence, withhold until recovery to Grade ≤ 2, then resume at 250 mg taken once daily ➤ Permanently discontinue in case of further Grade 4 recurrence

† Except lymphopenia.

References: 1. XALKORI® Summary of Product Characteristics 2013.

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.

References: 1. XALKORI® Summary of Product Characteristics 2013.

NEW XALKORI® CRIZOTINIB

Co-administration of XALKORI® with other medications

Agents whose plasma concentrations may be altered by XALKORI®

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

Coadministration 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.

If the combination is needed, then close clinical monitoring should be exercised.

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

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

- XALKORI® may induce PXR- and CAR-regulated enzymes*[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 altered

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

Exercise caution in administering XALKORI® in combination with medicinal products that are substrates of P-gp (e. g. digoxin, dabigatran, colchicine, pravastatin) — their therapeutic effect and adverse reactions of these agents may be increased

*In vitro data.

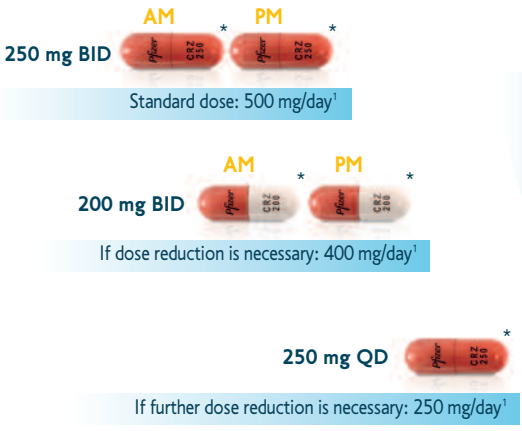
CYP3A, cytochrome P4503A; P-gp, permeability glycoprotein; PXR, pregnane X receptor; CAR, constitutive androstane receptor.

References: 1. XALKORI® Summary of Product Characteristics 2013.

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 reduction guidelines for haematologic and non-haematologic toxicities[1]

RECOMMENDED POSOLOGY[1]



*Capsules not shown in actual size.

BID, twice daily; QD, once daily. QTc, Q-T corrected.

References: 1. XALKORI® Summary of Product Characteristics 2013.

NEW XALKORI® CRIZOTINIB

XALKORI®

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

ADR Reporting
The Medicines Authority
Post-Licensing Directorate
203 Level 3, Rue D'Argens
GŻR-1368 Gżira
Website: www.medicinesauthority.gov.mt
e-mail: 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:
+30 210 67 85 908 and +30 210 67 85 808 (24-hour line).

For more information, please contact Pfizer Hellas S.A.
Medical Information at +30 210 67 85 800.

Local Representative: V.J. Salomone Pharma Ltd. Tel. +356 21220174

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

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