Crizotinib Monotherapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of adults with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).	C34	00243a	CDS
The treatment of adults with ROS1-positive advanced non-small cell lung cancer (NSCLC)	C34	00243b	Reimbursement not approved[i]
First-line treatment of adults with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)	C34	00243c	Reimbursement not approved[i]

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Crizotinib is administered daily until disease progression or unacceptable toxicity develops.

Drug	Dose	Route	Cycle
Crizotinib	250mg Twice Daily	PO With or without food	Continuous
Delayed or Missed Doses: If a dose 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			
The capsules should be swallowed whole, preferably with water, and should not be crushed, dissolved, or opened.			
Crizotinib is available as 200mg and250mg capsules.			

ELIGIBILTY:

- Indications as above
- ALK-positive and/or ROS1-positive NSCLC as demonstrated by an accurate and validated test method
- ECOG status 0-2

EXCLUSIONS:

- Hypersensitivity to crizotinib or to any of the excipients
- Patients with severe hepatic impairment
- Concomitant treatment with any other anticancer therapy
- QTc-interval longer than 500 milliseconds

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- Baseline confirmation that the patient's NSCLC tumour is ALK and/or ROS-1 positive by an accurate and validated test method.
- Blood, renal and liver profile
- Chest X-ray and CT scan
- ECG/QT interval evaluation for patients at risk.
- Clinical assessment, including evaluation for symptoms or signs of infection, pneumonitis, vision disorder, neuropathy, and oedema

Regular tests:

- LFTs and bilirubin every 2 weeks for first 2 months and then monthly.
- Blood and renal profile monthly.
- Chest X-ray monthly.
- ECG every 2 cycles, heart rate and blood pressure to monitor for cardiotoxicity as required.
- Clinical assessment, including evaluation for symptoms or signs of infection, pneumonitis, vision disorder, neuropathy, and oedema.

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant
- Dosing interruption and/or dose reduction may be required based on individual safety and tolerability.

Table 1: Dose reduction schedule for crizotinib

Level	Crizotinib Dose
Starting Dose	250mg Twice daily
1st Reduction	200mg Twice daily
2nd Reduction	250mg **once daily**

Haematological:

Table 2: Dose modification of crizotinib - Haematologial toxicities*

Level	Dose Modification
Grade 3	Withhold until recovery to Grade ≤ 2, then resume at the same dose schedule
Grade 4 1st occurrence	Withhold until recovery to Grade ≤ 2, then resume at **200 mg twice daily**
2nd occurrence	Dosing should be withheld until recovery to Grade ≤ 2, then dosing should be resumed at **250 mg once daily**.
3rd occurrence	DISCONTINUE crizotinib permanently.

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

Renal and Hepatic Impairment:

Table 3: Dose modification of crizotinib in renal and hepatic impairment

Renal Impairment		Hepatic Impairment			
CrCl (ml/min)	**Dose**	**AST**		**Total Bilirubin**	**Dose**
>30	No dose modification required	Any	and	>1.5 and ≤ 3 x ULN	200mg twice daily
<30	The crizotinib dose should be adjusted to 250 mg taken orally once daily in patients with severe renal impairment not requiring peritoneal dialysis or hemodialysis. The dose may be increased to 200 mg twice daily based on individual safety and tolerability after at least 4 weeks of treatment.	Any	and	>3 x ULN	250mg once daily

Management of adverse events:

Table 4: Dose modification schedule based on adverse events

Adverse reactions	Recommended dose modification
Grade ≥ 3 ALT or AST elevation with Grade ≤1 total bilirubin. 1st occurrence 2nd occurrence	 Withhold until recovery to Grade ≤ 1 or baseline, then resume at **250 mg once daily and escalate to 200mg twice daily if clinically tolerated** Permanently discontinue
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 hemolysis)	Permanently discontinue
Any Grade interstitial lung disease (ILD)pneumonitis[a]	Withhold if ILD/pneumonitis is suspected, and permanently discontinue if treatment-related ILD/pneumonitis is diagnosed
Grade 3 QTc prolongation	Withhold until recovery to Grade ≤1, check and if necessary correct electrolytes, then resume at 200 mg twice daily
Grade 4 QTc prolongation	Discontinue permanently
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 [a, b] Life threatening consequences, urgent intervention required	Permanently discontinue if no contributing concomitant medication is identified. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at 250mg once daily upon recovery to Grade≤1 or to heart rate 60 or above with frequent monitoring
Grade 4 Ocular Disorder (Visual Loss)	Discontinue during evaluation of severe vision loss

[a] Heart rate < 60 beats per minute (bpm) [b]Permanently discontinue for recurrence.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Moderate to high (**Refer to local policy).**

PREMEDICATIONS : Not required

OTHER SUPPORTIVE CARE: No specific recommendations

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Hepatoxicity:** Drug–induced hepatotoxicity with fatal outcome occurred in patients receiving crizotinib. 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. For people who develop transaminase elevations reference table 3.
- **Interstitial lung disease (ILD)/Pneumonitis:** Crizotinib has been associated with severe, life-threatening, or fatal treatment-related ILD/pneumonitis. These cases generally occurred within 2 months after the initiation of treatment. Patients should be regularly monitored for pulmonary symptoms indicative of ILD/pneumonitis.
- **Cardiac Failure:** Severe, sometimes fatal, cases of cardiac failure have been reported in patients with ALK-positive NSCLC treated with crizotinib. Cardiac failure occurred in patients with or without pre-existing cardiac disorders, receiving crizotinib. Patients should be monitored for signs and symptoms of heart failure (dyspnoea, oedema, rapid weight gain from fluid retention). If symptoms of cardiac failure are observed, appropriate measures such as dosing interruption, dose reduction, or discontinuation should be considered.
- **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. Crizotinib 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. When using crizotinib in these patients, periodic monitoring with electrocardiograms and electrolytes should be considered.
- **Bradycardia:** Treatment-emergent all-causality bradycardia was reported in clinical studies in 5 to 10% of patients treated with crizotinib. Symptomatic bradycardia (e.g., syncope, dizziness, hypotension) can occur in patients receiving crizotinib. 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 Table 3 under Dose Modifications.
- **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
- **Neutropenia and Leukopenia:** 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
- **Gastrointestinal perforation:** In clinical studies with crizotinib, events of gastrointestinal perforations were reported. There were reports of fatal cases of gastrointestinal perforation during post-marketing use of crizotinib.
- **Visual effects:** Vision disorder occurred in patients during clinical trials. In patients with new onset of severe visual loss (best corrected visual acuity less than 6/60 in one or both eyes), crizotinib 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 crizotinib in patients with a severe visual loss. A decision to resume crizotinib should consider the potential benefit to the patient.
Ophthalmological evaluation is recommended if vision disorder persists or worsens in severity.

DRUG INTERACTIONS:

- Crizotinib is a substrate and inhibitor of CYP3A. The concomitant use of crizotinib with strong CYP3A4 inhibitors or with strong and moderate CYP3A4 inducers should be avoided. The concomitant use of crizotinib with 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
- Current drug interaction databases should be consulted for more information

ATC CODE:

Crizotinib - L01XE16

REFERENCES:

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3. Crizotinib in advanced ROS1-rearranged non-small cell lung cancer (NSCLC): updated results from PROFILE 1001. Annals of Oncology 2016; 27 (Supplement 6): vi416–vi454.
4. Solomon BJ et al. First-Line Crizotinib versus Chemotherapy in ALK-Positive Lung Cancer. N Engl J Med 2014;371(23):2167-2177.
5. Important Safety Information communication from Pfizer Healthcare Ireland on the inclusion of a new warning regarding cardiac failure associated with Xalkori (crizotinib) Available at http://www.hpra.ie/docs/default-source/default-document-library/important-safety-information---xalkori-(crizotinib).pdf?sfvrsn=0
6. XALKORI® Summary of Product Characteristics. Last updated: 27/11/2019. Accessed Dec 2019. Available at https://www.ema.europa.eu/en/documents/product-information/xalkori-epar-product-information_en.pdf
7. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V1 2018. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp%20antiemetic%20classification%20document%20v1%202018.pdf

Version	Date	Amendment	Approved By
1	10/01/15		Dr Emer O Hanrahan
2	25/11/15	Update of Dose Modifications in renal impairment, adverse events particularly braycardia. Update of Adverse events/regimen specific complications to include information on risk of cardiac failure, bradycardia, neutropenia and leucopenia	Dr Maccon Keane
3	20/06/2016	Update of adverse events to include cardiac failure, gastrointestinal perforation and more information on visual effects	Dr Maccon Keane
4	20/12/2017	Addition of new Indications Update of emetogenic potential. Inclusion of company support resources. New NCCP regimen template applied	Prof Maccon Keane
5	26/01/2018	Update of dosing in hepatic impairment recommendations based on SmPC	Prof Maccon Keane
6	08/01/2020	Reviewed. Removed company support resources. Updated emetogenic potential.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] Post 2012 indication. Not reimbursed through the ODMS or Community Drug Schemes (including the High Tech arrangements of the PCRS community drug schemes). Please check https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/new.html for the most up to date reimbursement approvals.

ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes