Crizotinib Monotherapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Treatment of adults with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).	C34	00243a	CDS 01/06/2014
The treatment of adults with ROS1-positive advanced non-small cell lung cancer (NSCLC).	C34	00243b	N/A
First-line treatment of adults with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).	C34	00243c	N/A

* This is for post 2012 indications only.

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	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 with or without food, preferably with water, and should not be crushed, dissolved, or opened.			
Crizotinib is commonly available as 200mg and 250mg hard capsules and 20mg, 50mg and 150mg granules in capsules for opening.			

ELIGIBILITY:

- 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
- 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
- FBC, 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
- FBC 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***

*Permanently discontinue if unable to tolerate crizotinib 250 mg once daily

Haematological:

Table 2: Dose modification of crizotinib - Haematologial toxicities*

Grade	Dose Modification
Grade 3	Withhold until recovery to Grade ≤ 2, then resume at the same dose schedule
Grade 4	Withhold until recovery to Grade ≤2, then resume at the next lower dose[a,b]

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

[a]In case of recurrence, dosing should be withheld until recovery to Grade ≤2, then dosing should be resumed at 250 mg once daily. Crizotinib must be permanently discontinued in case of further Grade 4 recurrence

[b]For patients treated with 250mg once daily or whose dose was reduced to 250mg once daily, discontinue during evaluation

Renal and Hepatic Impairment:

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

Renal Impairment		Hepatic Impairment	
CrCl (mL/min)	**Dose**	**Level**	**Dose**
>30	No dose adjustment is needed	Mild	No dose adjustment is needed
<30	50% of the original dose	Moderate	80% of starting dose BD
Haemodialysis	A need for dose adjustment to 50% of the original dose is expected (250 mg QD)	Severe	50% of starting dose QC (250 mg QD), increase if tolerated
Renal and hepatic dose modifications from Giraud et al 2023			

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.	Withhold until recovery to Grade ≤ 1 or baseline, then resume at **250mg once daily and escalate to 200mg twice daily if clinically tolerated** [a,b]
Grade 2, 3 or 4 ALT or AST elevation with concurrent Grade 2, 3 or 4 total bilirubin elevation (in the absence of cholestasis or haemolysis)	Permanently discontinue
Any Grade interstitial lung disease (ILD)pneumonitis	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 200mg twice daily [a,b]
Grade 4 QTc prolongation	Discontinue permanently

Grade 2,3 Bradycardia[c] 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 [c,d] 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] Crizotinib must be permanently discontinued in case of further Grade ≥3 recurrence
[b] For patients treated with 250 mg once daily or whose dose was reduced to 250 mg once daily, discontinue during evaluation
[c] Heart rate < 60 beats per minute (bpm)
[d] Permanently discontinue for recurrence

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL

- As outlined in NCCP Classification Document for Systemic AntiCancer Therapy (SACT) Induced Nausea and Vomiting - Available on the NCCP website

Crizotinib: Moderate to high (**Refer to local policy).**

For information:
Within NCIS regimens, anti-emetics have been standardised by the Medical Oncologists and Haemato-oncologists and information is available in the following document:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - Available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - Available on the NCCP website

PREMEDICATIONS : Not required

OTHER SUPPORTIVE CARE: No specific recommendations

ADVERSE EFFECTS

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details.

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information.

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 Crizotinib (Xalkori®). Available at: http://www.hpra.ie/docs/default-source/default-document-library/important-safety-information---xalkori-(crizotinib).pdf?sfvrsn=0
6. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(23)00216-4/fulltext
7. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
8. Crizotinib (XALKORI®) Summary of Product Characteristics. Last updated: 27/08/2024. Accessed November 2024. Available at: https://www.ema.europa.eu/en/documents/product-information/xalkori-epar-product-information_en.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 bradycardia. 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
7	27/01/2025	Reviewed. Updated exclusions. Updated Table 2 Dose modification in Haematologial toxicities. Updated renal and hepatic dose modifications section to align with Giraud et al 2023. Update to Table 4: Dose modifications in adverse events. Updated regimen in line with NCCP standardisation.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.