Alectinib Monotherapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*Reimbursement status
Treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib	C34	00401a	CDS 01/11/2017
As monotherapy is indicated for the first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)	C34	00401b	CDS 01/06/2019

**If the reimbursement status is not defined, the indication has yet to be assessed through the formal HSE reimbursement process.*

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.

Alectinib is taken twice daily until disease progression or unacceptable toxicity develops.

Ensure a minimum 7 day washout after crizotinib prior to starting alectinib (indication 00401a)

Drug	Dose	Route	Cycle
Alectinib	600mg **BD**	PO Swallow whole. They must be taken with food.	Continuous
Delayed or Missed Doses: If a planned dose of alectinib is missed, patients can make up that dose unless the next dose is due within 6 hours. Patients should not take two doses at the same time to make up for a missed dose. **Vomiting:** If vomiting occurs after taking a dose of alectinib, patients should take the next dose at the scheduled time.			
Alectinib is available as 150mg capsules. The capsules must not be opened or dissolved			

ELIGIBILTY:

- Indication as above
- Histologically confirmed, advanced NSCLC with an ALK rearrangement by an approved and validated test method
- ECOG 0-2
- Adequate organ function

EXCLUSIONS:

- Hypersensitivity to alectinib or to any of the excipients

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 positive by an accurate and validated test method.
- Blood, renal and liver profile
- Chest X-ray and CT scan
- Blood Pressure
- ECG

Regular tests:

- Liver profile every 2 weeks during the first 3 months of treatment and every 4 weeks thereafter
- Blood and renal profile every 4 weeks
- CPK every 2 weeks for first month and then as clinically indicated
- ECG every 4 weeks

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
- Management of adverse events may require dose reduction, temporary interruption, or discontinuation of treatment with alectinib.
- The dose of alectinib should be reduced in steps of 150 mg twice daily based on tolerability (Table 1).
- Alectinib treatment should be permanently discontinued if patients are unable to tolerate the 300 mg twice daily dose.

Table 1: Dose reduction schedule for alectinib

Dose Reduction Schedule	Dose Level
Starting dose	600mg twice daily
First dose reduction	450mg twice daily
Second dose reduction	300mg twice daily

Renal and Hepatic Impairment:

Table 2: Dose modification of alectinib in renal and hepatic impairment

Renal Impairment	Hepatic Impairment
No dose adjustment is required in patients with mild or moderate renal impairment. Alectinib has not been studied in patients with severe renal impairment. However, since alectinib elimination via the kidney is negligible, no dose adjustment is required in patients with severe renal impairment	No starting dose adjustment is required in patients with underlying mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. Patients with underlying severe hepatic impairment (Child-Pugh C) should receive a starting dose of 450 mg taken twice daily (total dose of 900 mg)

Management of adverse events:

Table 3: Dose modification schedule based on adverse events

CTCAE Grade	Dose Modification
ILD/pneumonitis of any severity grade	Immediately interrupt and permanently discontinue alectinib if no other potential causes of ILD/pneumonitis have been identified
ALT or AST elevation of Grade ≥ 3 (> 5 times ULN) with total bilirubin ≤ 2 times ULN	Temporarily withhold until recovery to baseline or ≤ Grade 1 (≤ 3 times ULN), then resume at reduced dose (see Table 1).
ALT or AST elevation of Grade ≥ 2 (> 3 times ULN) with total bilirubin elevation > 2 times ULN in the absence of cholestasis or haemolysis	Permanently discontinue alectinib.
Bradycardia[a] Grade 2 or Grade 3 (symptomatic, may be severe and medically significant, medical intervention indicated)	Temporarily withhold until recovery to ≤ Grade 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm. Evaluate concomitant medicinal products known to cause bradycardia, as well as anti-hypertensive medicinal products. • If a contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, resume at previous dose upon recovery to ≤ Grade 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm. • If no contributing concomitant medicinal product is identified, or if contributing concomitant medicinal products are not discontinued or dose modified, resume at reduced dose (see Table 1) upon recovery to ≤ Grade 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm.
Bradycardia[a] Grade 4 (life-threatening consequences, urgent intervention indicated)	• Permanently discontinue if no contributing concomitant medicinal product is identified. • If a contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, resume at reduced dose (see Table 1) upon recovery to ≤ Grade 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm, with frequent monitoring as clinically indicated. • Permanently discontinue in case of recurrence.
CPK elevation > 5 times ULN	Temporarily withhold until recovery to baseline or to ≤ 2.5 times ULN, then resume at the same dose
CPK elevation > 10 times ULN or second occurrence of CPK elevation of > 5 times ULN	Temporarily withhold until recovery to baseline or to ≤ 2.5 times ULN, then resume at reduced dose as per Table 1.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; CTCAE = NCI Common Terminology Criteria for Adverse Events; ILD = interstitial lung disease; ULN = upper limit of normal

[a] Heart rate less than 60 beats per minute (bpm).

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Low (**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.

This medicinal product is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

- **Interstitial lung disease (ILD)/pneumonitis**: Cases of ILD/pneumonitis have been reported in clinical trials with Alectinib. Patients should be monitored for pulmonary symptoms indicative of pneumonitis. Alectinib should be immediately interrupted in patients diagnosed with ILD/pneumonitis and should be permanently discontinued if no other potential causes of ILD/pneumonitis have been identified**.**
- **Hepatotoxicity:** Liver function, including ALT, AST, and total bilirubin should be monitored at baseline and then every 2 weeks during the first 3 months of treatment. Thereafter, monitoring should be performed periodically, since events may occur later than 3 months, with more frequent testing in patients who develop aminotransferase and bilirubin elevations. Based on the severity of the adverse drug reaction, alectinib should be withheld and resumed at a reduced dose, or permanently discontinued as described in Table 1.
- **Severe myalgia and creatine phosphokinase (CPK) elevation:** Patients should be advised to report any unexplained muscle pain, tenderness, or weakness. CPK levels should be assessed every two weeks for the first month of treatment and as clinically indicated in patients reporting symptoms. Based on the severity of the CPK elevation, alectinib should be withheld, then resumed or dose reduced.
- **Bradycardia:** Symptomatic bradycardia can occur with alectinib. Heart rate and blood pressure should be monitored as clinically indicated. Dose modification is not required in case of asymptomatic bradycardia. If patients experience symptomatic bradycardia or life-threatening events, concomitant medicinal products known to cause bradycardia, as well as anti-hypertensive medicinal products should be evaluated and alectinib treatment should be adjusted as described in Table 3.
- **Photosensitivity:** Photosensitivity to sunlight has been reported with alectinib administration Patients should be advised to avoid prolonged sun exposure while taking alectinib, and for at least 7 days after discontinuation of treatment. Patients should also be advised to use a broad-spectrum Ultraviolet A (UVA)/ Ultraviolet B (UVB) sun screen and lip balm (SPF ≥50) to help protect against potential sunburn.
- **Women of child-bearing potential:** Alectinib may cause foetal harm when administered to a pregnant woman. Female patients of child-bearing potential receiving alectinib, must use highly effective contraceptive methods during treatment and for at least 3 months following the last dose of alectinib.
- **Lactose intolerance**: This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, a congenital lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
- **Sodium content:** This medicinal product contains 48 mg sodium per daily dose (1200 mg), equivalent to 2.4% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

DRUG INTERACTIONS:

- Based on in vitro data, CYP3A4 is the primary enzyme mediating the metabolism of both alectinib and its major active metabolite M4, and CYP3A contributes to 40% – 50% of total hepatic metabolism.
  - Appropriate monitoring is recommended for patients taking concomitant strong CYP3A inducers and inhibitors
- Caution with BCRP and P-glycoprotein substrates with a narrow therapeutic index (in vitro increases in substrate concentration).
- Current drug interaction databases should be consulted for more information

ATC CODE:

Alectinib - L01XE36

REFERENCES:

1. Ou et al. Alectinib in Crizotinib-Refractory ALK-Rearranged Non–Small-Cell Lung Cancer: A Phase II Global Study. J Clin Oncol 2015;34:661-668.
2. Shaw AT et al. Phase 2 prospective analysis of alectinib in *ALK*-positive, crizotinib-resistant non-small-cell lung cancer Lancet Oncol. 2016 ; 17(2): 234–242
3. Yang et al. Pooled Systemic Efficacy and Safety Data from the Pivotal Phase II Studies (NP28673 and NP28761) of Alectinib in ALK-positive Non-Small Cell Lung Cancer. J Thoracic Oncology 2017;
4. Peters et al. Alectinib versus Crizotinib in Untreated ALK-Positive Non Small-Cell Lung Cancer. NEJM 2017; 377(19) 829-838.
5. Alecesa Summary of Product Characteristics. Accessed Feb 2019 Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004164/WC500225707.pdf

Version	Date	Amendment	Approved By
1	26/09/17		Dr. Deirdre O'Mahony
2	01/11/2017	Updated reimbursement status	
3	21/01/2019	Updated hepatic impairment dose modifications as per SmPC update.Adverse Events : Updated wording on sodium content as per SmPC update	Dr. Deirdre O'Mahony
4	13/06/2019	Inclusion of indication for 1L treatment	Dr Dearbhaile Collins

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes
Further details on the Cancer Drug Management Programme is available at;
http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/