Ceritinib 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	00340a	CDS

**If the reimbursement status is not defined [1], 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.

Ceritinib is administered once daily until disease progression or unacceptable toxicity develops.

Drug	Dose	Route	Cycle
Ceritinib	450mg daily	PO with food	Continuous
The capsules should be swallowed whole, preferably with water, and should not be crushed.			
Missed Dose: If a dose is missed, the patient should make up that dose, unless the next dose is due within 12 hours.			
Vomiting: If vomiting occurs during a course of treatment the patient should not take an additional dose but should continue with the next scheduled dose			
The maximum recommended dose with food is 450 mg taken orally once daily			

ELIGIBILTY:

- Indications as above
- ALK-positive NSCLC as demonstrated by an accurate and validated test method
- ECOG status 0-2
- Adequate organ function

CAUTION in USE:

- For patients who develop a concurrent medical condition and are unable to take ceritinib with food, ceritinib may be taken on an empty stomach in which no food should be eaten for at least two hours before and one hour after the dose.
  - Patients should not alternate between fasted and fed dosing
  - Dose must be adjusted properly, i.e
    - for patients treated with 450 mg with food, the dose should be increased to 750 mg taken on an empty stomach
    - for patients treated with 300 mg with food the dose should be increased to 450 mg taken on an empty stomach,
    - for patients treated with 150 mg with food treatment should be discontinued
  - This is for those patients unable to take ceritinib with food only
  - The maximum allowed dose under fasted conditions is 750 mg.

EXCLUSIONS:

- Patients with hypersensitivity to ceritinib or any of its listed excipients
- Patients with ALK-negative NSCLC
- Patients with moderate or severe hepatic impairment
- Patients with congenital long QT syndrome or with a persistent QTcF > 500 milliseconds
- Pregnancy or lactation

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.
- FBC, renal and liver profile
- Lipase and amylase
- Fasting glucose
- ECG/QT interval evaluation
- Clinical toxicity assessment, including evaluation for gastrointestinal, pancreatic, cardiac (heart rate, blood pressure), and respiratory symptoms.

Regular tests:

- FBC and renal profile every 4 weeks.
- Liver profile every 2 weeks for first month and then every 4 weeks.
- Fasting glucose every 4 weeks. More frequent monitoring required if abnormal or if pre-existing diabetes.
- ECG every 4 weeks for first 3 months of treatment. More frequent monitoring required in patients at risk for QTc prolongation and in patients who develop prolonged QTc or bradycardia on treatment (see Table 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.
- **Temporary dose interruption and/or dose reduction of ceritinib may be required based on individual safety and tolerability**
- Ceritinib should be discontinued in patients unable to tolerate 150mg daily taken with food.
- Reduced doses should not be re-escalated. If doses are held longer than 3 weeks for toxicity, consider discontinuation

Table 2: Dose reduction steps for ceritinib

Level	Ceritinib Dose*
Starting Dose	450mg daily
1st Reduction	300mg daily
2nd Reduction	150mg daily
3rd Reduction	Discontinue

***Dose reduction steps for ceritinib in those patients unable to take ceritinib with food are outlined under caution in use**

Renal and Hepatic Impairment:

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

Renal impairment	Hepatic Dysfunction
No dose adjustment is necessary in patients with mild to moderate renal impairment. Caution should be used in patients with severe renal impairment as there is no experience with	Ceritinib is eliminated primarily via the liver. No dose adjustment is necessary in patients with mild or moderate hepatic impairment. Particular caution should be exercised when treating patients with severe hepatic impairment and the dose should be reduced by approximately one third, rounded to the nearest multiple of the 150 mg dosage strength.

Adverse Events:

Table 4: Dose modification schedule for ceritinib based on adverse events

Adverse reactions	Recommended dose modification
AST or ALT > 5 x ULN and total bilirubin ≤ 2 x ULN	Hold until recovery to baseline or ≤ 3 x ULN, then reinitiate ceritinib with dose reduced by 150mg
ALT or AST elevation >3 times ULN with concurrent total bilirubin elevation >2 times ULN (in the absence of cholestasis or haemolysis)	Permanently discontinue
Any Grade treatment related interstitial lung disease(ILD)/pneumonitis	Permanently discontinue

QT corrected for heart rate (QTc) >500 msec on at least 2 separate electrocardiograms (ECGs)	Withhold until recovery to baseline or to a QTc ≤480 msec, check and if necessary correct electrolytes, then reinitiate with dose reduced by 150mg
QTc >500 msec or >60 msec change from baseline and torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	Permanently discontinue
Bradycardia[a] (symptomatic, may be severe and medically significant, medical intervention indicated)	Withhold ceritinib until recovery to asymptomatic (grade ≤1) bradycardia or to a heart rate of 60 beats per minute (bpm) or above. 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, reinitiate ceritinib at the previous dose upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. If no contributing concomitant medicinal product is identified, or if contributing concomitant medicinal products are not discontinued or dose modified, reinitiate ceritinib with dose reduced by 150mg upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above
Bradycardia (life-threatening consequences, urgent intervention indicated)	Permanently discontinue ceritinib if no contributing concomitant medicinal product is identified. If a contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, reinitiate ceritinib with dose reduced by 150mg upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring[b].
Severe (grade 3) or intolerable nausea, vomiting or diarrhoea despite optimal anti-emetic or anti-diarrhoeal therapy	Withhold until improved, then reinitiate ceritinib with dose reduced by 150mg.
Persistent hyperglycaemia greater than 250 mg/dl despite optimal anti-hyperglycaemic therapy	Withhold until hyperglycaemia is adequately controlled, then reinitiate ceritinib with dose reduced by 150mg. If adequate glucose control cannot be achieved with optimal medical management, permanently discontinue ceritinib
Lipase or amylase elevation grade ≥3	Withhold ceritinib until lipase or amylase returns to grade ≤1, then reinitiate with dose reduced by 150mg.

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

Dose modification for pharmacokinetic reasons:

- Avoid concomitant use of strong CYP3A inhibitors during treatment with ceritinib.
- If concomitant use of a strong CYP3A inhibitor is unavoidable, reduce the dose by

approximately one third, rounded to the nearest multiple of the 150 mg dosage strength.

- Patients should be carefully monitored for safety.
- If long-term concomitant treatment with a strong CYP3A inhibitor is necessary and the patient tolerates the reduced dose well, the dose may be increased again with careful monitoring for safety, to avoid potential under-treatment.
- After discontinuation of a strong CYP3A inhibitor, resume at the dose that was taken prior to initiating the strong CYP3A inhibitor

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Low (Refer to local policy).

PREMEDICATIONS:

Not usually required

OTHER SUPPORTIVE CARE:

Ceritinib has minor influence on the ability to drive or use machines. Caution should be exercised when driving or using machines during treatment as patients may experience fatigue or vision disorders.

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. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

- Hepatoxicity: Increases to grade 3 or 4 ALT elevations were observed in 25% of patients. The majority of cases were manageable with dose interruption and/or dose reduction. Few events required discontinuation of treatment.
- Interstitial lung disease (ILD)/Pneumonitis: Severe, life-threatening or fatal interstitial lung disease (ILD) / pneumonitis have been observed in patients treated with ceritinib in clinical studies. Most cases improved or resolved with interruption of treatment. Patients should be monitored for pulmonary symptoms indicative of pneumonitis. Other potential causes of pneumonitis should be excluded, and ceritinib permanently discontinued in patients diagnosed with treatment-related pneumonitis
- QT interval prolongation: QTc prolongation has been observed in clinical studies in patients treated with ceritinib which may lead to an increased risk for ventricular tachyarrhythmias (e.g. torsade de pointes) or sudden death. Ceritinib should be avoided in patients with congenital long QT syndrome. Periodic monitoring with ECG and electrolytes is recommended in patients at risk of QTc prolongation:
    - Pre-existing bradycardia
    - History of or predisposition to QTc prolongation
    - Taking antiarrhythmics or other medicinal products that are known to prolong QT interval
    - Pre-existing cardiac disease and / or electrolyte disturbances
    - Patients with vomiting, diarrhoea, dehydration or impaired renal function.

  Ceritinib with-holding and/or dose modification is required for prolongation of QTc, as per table 4 above.

- Bradycardia: Ceritinib should be used with caution in patients with baseline bradycardia (HR < 60 bpm), history of syncope or arrhythmia, sick sinus syndrome, sinoatrial block, atrioventricular block, ischemic heart disease or congestive heart failure. Use of ceritinib in combination with other agents known to cause bradycardia (e.g. beta blockers, non-dihydropyridine calcium channel blockers, clonidine and digoxin) should be avoided as far as possible. Heart rate and blood pressure should be monitored regularly. Ceritinib with-holding and/or dose modification is required for bradycardia, as per table 2 above.
- Hyperglycaemia: Hyperglycaemia has been reported and may be severe. Risk is higher in patients with diabetes and/or concurrent steroid use. Patients should be monitored for fasting plasma glucose prior to the start of ceritinib treatment and periodically thereafter as clinically indicated. Anti-hyperglycaemic medicinal products should be initiated or optimised as indicated.
- Lipase and/or amylase elevations: Patients should be monitored for lipase and amylase elevations prior to the start of treatment and periodically thereafter as clinically indicated. Cases of pancreatitis have been reported in patients treated with ceritinib

DRUG INTERACTIONS:

- Current drug interaction databases should be consulted for more information.
- Ceritinib is primarily metabolized by CYP3A, may inhibit CYP3A, CYP2C9, CYP2A6 and CYP2E1, and is a substrate of P-gp. Concomitant administration of ceritinib and strong CYP3A inhibitors should be avoided if possible. If necessary the dose of ceritinib should be modified as described under dose modifications for pharmacokinetic reasons. Patients should also be counselled with regard to consumption of grapefruit and grapefruit juice.
- Ceritinib is a substrate for P-gp. If ceritinib is administered with medicinal products that inhibit P-gp, an increase in ceritinib concentration is likely. Caution should be exercised with concomitant use of P-gp inhibitors and adverse drug reactions carefully monitored.
- Co-administration of ceritinib with strong CYP3A/P-gp inducers decreases ceritinib plasma concentrations. Concomitant use of strong CYP3A inducers should be avoided Caution should be exercised with concomitant use of P-gp inducers
- Concomitant ceritinib may increase the concentration / toxicity of CYP3A substrates (e.g. cyclosporine, tacrolimus, dihydropyridine calcium-channel blockers, certain HMG-CoA reductase inhibitors) and CYP2C9 substrates (e.g. warfarin). Concomitant use with substrates that have narrow therapeutic indices should be avoided.
- Gastric acid-reducing agents (e.g. proton pump inhibitors, H2-receptor antagonists, antacids) may alter the solubility of ceritinib and reduce its bioavailability as ceritinib demonstrates pH-dependent solubility.
- Concomitant use of drugs that may prolong QT (including, but not limited to, amiodarone, procainamide, sotalol, venlafaxine, amitriptyline, haloperidol, clarithromycin, moxifloxacin, fluconazole, domperidone, ondansetron) should be avoided if possible. If necessary monitor QTc interval regularly.
- Caution is required with concomitant use of ceritinib and drugs that affect electrolyte levels (e.g. diuretics, laxatives, high dose corticosteroids) as this can also prolong the QT interval. Electrolytes should be monitored and corrected regularly.
- Drugs that lower the heart rate (e.g. beta blockers, calcium channel blockers, digoxin) increase the risk of bradycardia. Avoid concomitant use if possible. Closely monitor heart rate and blood pressure.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Ceritinib - L01XE28

REFERENCES:

1. Shaw AT, Kim D-W, Mehra R, Tan DS, Felip E, Chow LQ, et al. Ceritinib in ALK-rearranged non-small-cell lung cancer. N Engl J Med 2014;370:1189-1197
2. Felip E, Dong-Wan K, Mehra R, Tan DSW, Chow LQM, Camidge R, et al. Efficacy and safety of ceritinib in patients with advanced anaplastic lymphoma kinase (ALK)-rearranged (ALK+) non-small cell lung cancer (NSCLC): an update of ASCEND-1. Poster presented at: European Society for Medical Oncology (ESMO); 2014; Sept 26-30; Madrid, Spain.
3. Mok T, Spigel D, Felip E, De Marinis F, Ahn M-J, Groen HJM, et al. ASCEND-2: A single-arm, open-label, multicenter phase II study of ceritinib in adult patients (pts) with ALK-rearranged (ALK+) non-small cell lung cancer (NSCLC) previously treated with chemotherapy and crizotinib (CRZ) [abstract]. J Clin Oncol. 2015;33(suppl; abstr 8059). (Presented at 2015 ASCO Annual Meeting; May 29-June 2, 2015; Chicago, Illinois)
4. ASCEND-3: A single-arm, open-label, multicenter phase II study of ceritinib in ALKi-naïve adult patients (pts) with ALK-rearranged (ALK+) non-small cell lung cancer (NSCLC). Filip E et al, J Clin Oncol 33, 2015 (suppl; abstr 806)
5. Zykadia ® Summary of Product Characteristics Accessed Dec 2018. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003819/WC500187504.pdf

Version	Date	Amendment	Approved By
1	20/12/16		Dr Emer O Hanrahan
2	15/10/2018	Updated with new NCCP regimen template Updated daily dose as per SmPC and dosing in severe renal hepatic impairment as per SmPC update	Dr Emer O Hanrahan

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/