CERITINIB

For the treatment of anaplastic lymphoma kinase (ALK) +ve advanced NSCLC patients previously treated with crizotinib (NICE approved June 2016)

Blueteq registration is required before treatment may start

Drug/Dosage: **Ceritinib** initiate at 750mg po once daily as continuous therapy

Administration: Ceritinib is available as 150mg capsules.
The capsules should be swallowed whole with some water at about the same time each day. They must be taken on an empty stomach; no food for at least 2 hours before and until 2 hours after the dose is taken. (bioavailability is increased in the presence of food)
Grapefruit and grapefruit juice should be avoided while on ceritinib.

Frequency: continuous therapy until progression or unacceptable toxicity
2 week toxicity check required, to include LFTs

Main Toxicities: diarrhoea or constipation; rash; increased LFTs; fatigue; loss of appetite; anaemia

Anti- emetics: nausea and vomiting is common; ensure patients have a supply of anti-emetics

Regular Investigations:		
	FBC	every 4 weeks
	LFTs	every 2 weeks for the first month, then monthly
	U&Es	every 4 weeks
	Glucose	baseline, then as indicated
	CT scan	every 3 months
	ECG / QTc	required for patients at risk only; check pre-treatment, then after 1 month, then as indicated (see Dose Modifications)
	Pulse	as indicated (see Bradycardia below)

Interactions: CYP3A is the major enzyme involved in the metabolic clearance of ceritinib.

Co-administration of ceritinib with strong CYP3A inhibitors (e.g. itraconazole, posaconazole, voriconazole, clarithromycin) should be avoided.
If this is not possible, reduce the ceritinib dose by approximately one third, rounded to the nearest multiple of the 150 mg dosage strength. After discontinuation of a strong CYP3A inhibitor, resume the ceritinib dose that was taken prior to initiating the strong CYP3A inhibitor.
Grapefruit should also be avoided for this reason.

Concomitant use of strong CYP3A inducers (e.g. phenytoin, rifampicin, carbamazepine, barbiturates, St John's Wort) with ceritinib should be avoided, as this may increase the risk of therapeutic failure.

Proton pump inhibitors, H_2-receptor antagonists, antacids may alter the solubility of ceritinib and reduce its bioavailability as ceritinib becomes poorly soluble as pH increases *in vitro*. Avoid concomitant use if possible.

Dose Modifications If dose reduction is required due to any adverse reaction, then this should be achieved by decrements of 150 mg daily.
Ceritinib should be discontinued in patients unable to tolerate 300 mg daily.

Reason for Update: need for blueteq registration added	Approved by Consultant: Dr V Ezhil
Version: 2	Approved by Lead Chemotherapy Nurse: P Deery
Supersedes: Version 1	Date: 19.1.17
Prepared by: S Taylor	Checked by: C Tucker

Nausea, vomiting or diarrhoea: If Grade 3, or intolerable, nausea, vomiting or diarrhoea despite optimal anti-emetic or anti-diarrhoeal therapy, withhold ceritinib until improved, then re-start with dose reduced by one decrement.

QT Prolongation: As QTc prolongation has been observed, ceritinib should be administered with caution to patients who have a history of or predisposition for QTc prolongation, or who are taking other medicines known to prolong the QT interval. When using ceritinib in these patients, periodic monitoring with ECGs and electrolytes is advised.

QTc interval (milliseconds)	Management
> 500 ms on at least 2 separate ECGs	Withhold ceritinib until recovery or QTc ≤ 480 ms. Check and if necessary correct electrolytes, then re-start with ceritinib dose reduced by one decrement.
> 500 ms or > 60 msec change from baseline **and** accompanied by life-threatening signs, or Torsade de pointes	Permanently discontinue ceritinib

Bradycardia:

Grade 2 or 3 Pulse less than 60 beats per minute (bpm) Symptomatic, may be severe and medically significant, medical intervention indicated	Withhold ceritinib until asymptomatic and heart rate ≥ 60 bpm. 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 ceritinib at previous dose upon recovery. If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, resume with dose reduced by one decrement upon recovery.
Grade 4 Pulse less than 60 bpm Life-threatening consequences, urgent intervention indicated	Permanently discontinue ceritinib if no contributing concomitant medication is identified. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume ceritinib with dose reduced by one decrement, with frequent monitoring, upon recovery and heart rate ≥ 60 bpm.

Hyperglycaemia: If persistent hyperglycaemia > 14mmol/l despite optimal anti-hyperglycaemic therapy, withhold ceritinib until hyperglycaemia is adequately controlled, then re-start with dose reduced by one decrement. If adequate glucose control cannot be achieved with optimal medical management, permanently discontinue ceritinib.

Pneumonitis: Ceritinib should be withheld if pneumonitis is suspected, and must be permanently discontinued if treatment-related pneumonitis is diagnosed.

Pancreatitis: If lipase or amylase elevation to Grade 3 or 4, withhold ceritinib until lipase or amylase returns to grade ≤1, then re-start with dose reduced by one decrement.

Hepatic Impairment: No dose adjustment is required in patients with mild hepatic impairment. It is not recommended in patients with moderate or severe hepatic impairment.

During treatment, if ALT or AST rises to > 5 x ULN with bilirubin ≤ 2 x ULN, withhold ceritinib until ALT / AST ≤ 3 x ULN, then re-start with one dose decrement.
If ALT or AST > 3 x ULN and bilirubin > 2 x ULN (in the absence of cholestasis or haemolysis), permanently discontinue ceritinib.

Renal Impairment: No dose adjustment is necessary in patients with CrCl ≥ 30ml/min. Caution should be used in patients with CrCl < 30ml/min as there is no experience with ceritinib in this population.