

## Dose reductions and management of adverse reactions to Ceritinib

Adverse event	Level / grade	Management
QTc prolongation	QTc interval (milliseconds) > 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.
	QTc interval (milliseconds) > 500 ms or > 60 msec change from baseline <b>and</b> 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	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	Suspected	Ceritinib should be withheld
	Treatment-related pneumonitis confirmed	Permanently discontinue
Pancreatitis	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.
Nausea, vomiting or diarrhoea	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.

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Version 1 (15/09/2016)

N.B. Version numbers re-started from 1 when adverse reaction information separated from proforma