Indication	The treatment of chronic phase, accelerated phase or blast phase chronic myeloid leukaemia in patients where the disease is resistant to dasatinib or nilotinib, or the patient cannot have dasatinib nor nilotinib and imatinib is not clinically appropriate, or the T315I gene mutation is present.
Treatment Intent	Curative Non-curative Remission
Frequency and number of cycles	Repeat every 30 days Continuously until disease progression or intolerable toxicity

Monitoring Parameters pre-treatment	• FBC every 2 weeks for the first 3 months then before each dispensing episode or as clinically indicated.
	• LFTs & U&Es required before cycle 1, and then before each dispensing episode or as clinically indicated.
	• If ANC $\geq$1.0x10^9/l and platelets $\geq$50 x10^9/l proceed with treatment.
	• If blood parameters are not met, then dose modifications are as follows:
	  ○ **First occurrence:** Withhold ponatinib and resume initial 45mg dose after recovery to ANC ≥1.5 x 10^9/L and platelet ≥75 x 10^9/L
	  ○ **Recurrence at 45mg:** Withhold ponatinib and resume at 30mg after recovery to ANC ≥1.5 x 10^9/L and platelet ≥75 x 10^9/L
	  ○ **Recurrence at 30mg:** Withhold ponatinib and resume at 15mg after recovery to ANC ≥1.5 x 10^9/L and platelet ≥75 x 10^9/L
	• Check virology status prior to cycle 1.
	• **Ponatinib** starting dose is **45mg OD, dose** can be reduced to 30mg or 15mg OD. Dose can be re-escalated once adverse reactions have been resolved.
	• **Consider discontinuing ponatinib if a complete haematologic response has not occurred by 3 months (90 days).**
	• **Drug interactions:**
	• Caution should be exercised with concurrent use of ponatinib and moderate and strong CYP3A inhibitors (e.g. clarithromycin, erythromycin, itraconazole) and moderate and strong CYP3A inducers (e.g. carbamazepine, dexamethasone and phenytoin).
	• Close clinical surveillance is recommended when ponatinib is administered with substrates of P-gp (e.g. digoxin, dabigatran, colchicine, pravastatin) or BCRP (e.g. methotrexate, rosuvastatin, sulfasalazine).
	• Concomitant use of ponatinib with anti-coagulants should be approached with caution in patients who may be at risk of bleeding events.
	• Grapefruit and grapefruit juice should be avoided while on ponatinib.
	• Use with St Johns Wort is contraindicated.
	• **Renal and hepatic impairment**
	• No dose adjustment is recommended for renal impairment. Use with caution in patients with CrCl <50ml/min
	• No dose adjustment is required in hepatic impairment although caution is recommended. See below under hepatic toxicity for advice.
	Adverse Reactions
	Pancreatitis:
	• The frequency of pancreatitis is greater in the first 2 months of use. Check serum lipase every 2 weeks for the first 2 months and then periodically thereafter. Dose interruption or reduction may be required.

	• Grade 3 or 4 asymptomatic elevation of lipase/amylase (> 2.0 x ULN) only: If occurrence at 45 mg, withhold and resume at 30 mg after recovery to ≤ Grade 1 (< 1.5 x ULN). If occurrence at 30 mg, withhold and resume at 15 mg after recovery to ≤ Grade 1 (< 1.5 x ULN). If occurrence at 15 mg, consider discontinuation. • Grade 3 pancreatitis: If occurrence at 45 mg, withhold and resume at 30 mg after recovery to < Grade 2. If occurrence at 30 mg, withhold and resume at 15 mg after recovery to < Grade 2. If occurrence at 15 mg, consider discontinuation. • Grade 4 pancreatitis - discontinue **Hypertension and cardiac disorders:** • Hypertension should be medically controlled during ponatinib treatment, interruption of which should be considered if hypertension is not controlled. • Ponatinib should not be used in patients with a history of MI or stroke, unless the potential benefit of treatment outweighs the potential risk. • Cardiovascular risk factors should be actively managed before starting treatment, and should continue to be optimised during treatment. • Patients should be monitored for signs and symptoms of congestive heart failure, treat as indicated, including interruption or discontinuation. **Vascular occlusion:** • Patients should be monitored for evidence of vascular occlusion or thromboembolism, and treatment should be interrupted immediately if this occurs. • A benefit-risk consideration should guide a decision to restart ponatinib. • The risk of arterial occlusive events is likely to be dose-related. Reducing the dose to 15 mg should be considered for CP-CML patients who have achieved a major cytogenetic response. **Hepatic Toxicity:** • Ponatinib may result in elevation in ALT, AST, bilirubin, and alkaline phosphatase. Hepatic failure (including fatal outcome) has been observed. • Elevation of liver transaminase > 3 × ULN / Persistent grade 2 (longer than 7 days) / Grade 3 or higher: If occurs at 45 mg, interrupt and monitor. Resume at 30 mg after recovery to ≤ Grade 1 (< 3 × ULN), or recovery to pre-treatment grade. If occurs at 30 mg, interrupt and resume at 15 mg after recovery to ≤ Grade 1, or recovery to pre-treatment grade. If occurs at 15 mg, discontinue. • Elevation of AST or ALT ≥ 3 × ULN concurrent with an elevation of bilirubin > 2 × ULN and alkaline phosphatase < 2 × ULN – discontinue. **Posterior reversible encephalopathy syndrome:** • Interrupt treatment if posterior reversible encephalopathy syndrome (PRES) is confirmed and resume treatment only once the event is resolved and the benefit of continued treatment outweighs the risk of PRES. **Severe Cutaneous Adverse Reactions (SCARs)** • Patients should be informed of the possibility of severe skin reactions such as Stevens-Johnson syndrome and informed to seek urgent medical advice should any symptoms of a severe skin reaction occur.
References	KMCC SACT proforma HAEM-CML-006 v2 MHRA update OCT 20 "Ponatinib (Iclusig▼): reports of posterior reversible encephalopathy syndrome" SPC accessed 09/11/2018

NB For funding information, refer to CDF and NICE Drugs Funding List

Repeat every 30 days

Day	Drug	Dose	Route	Administration
Day 1	**PONATINIB**	**45mg**	PO	Once Daily. Do not chew or crush. Swallow whole with water. Do not take with grapefruit juice. (available as 15mg, 30mg and 45mg tablets) This medicine may make you sleepy. If this happens, do not drive or use tools or machines
	Metoclopramide	10mg	PO	Take 10mg TDS PRN. Do not take for more than 5 days continuously.