PONATINIB

1. For use in adults with chronic phase CML, only if the T315I mutation is present (NICE 2017)
2. For use in adults with accelerated or blast phase CML where the disease is resistant to dasatinib or nilotinib, ***or*** the patient cannot tolerate dasatinib nor nilotinib and imatinib is not clinically appropriate, ***or*** with the T315I gene mutation (NICE 2017)
3. For use in Ph +ve ALL where the disease is resistant to dasatinib ***or*** the patient cannot tolerate dasatinib and imatinib is not clinically appropriate ***or*** the T315I gene mutation is present (NICE 2017)

Blueteq registration is required before patients may start treatment.

All patients should be screened for hepatitis B virus before starting treatment
This screen must include HBV surface antigen and anti-HBV core antibody

Drug/Dosage:	**Ponatinib** initiate at 45mg po once daily	
	Evidence shows that risk of arterial occlusion with ponatinib is likely to be dose-dependent; therefore prescribers should consider reducing the dose of ponatinib to 15 mg po once daily for patients with chronic phase CML who have achieved a major cytogenetic response	
Administration:	Ponatinib available as 45mg and 15mg tablets, which are not scored or divisible. Tablets should be swallowed whole, with or without a meal, at the same time of day each day. Grapefruit and grapefruit juice should be avoided while on ponatinib.	
Other Drugs:	Allopurinol 300mg po od for the first four weeks (may be omitted in the context of treatment change in patients with good haematological disease control)	
Frequency:	continuous therapy, until disease progression or no longer tolerated	
Main Toxicities:	myelosuppression; rash; vascular occlusion events (central and peripheral); pancreatitis; abdominal pain; hypertension; raised transaminases; headache; oedema; diarrhoea; arthralgia/myalgia	
Anti- emetics:	none usually needed, but some patients may have mild nausea	
Regular Investigations:	FBC	every 2 weeks for the first 3 months, then monthly, then increasing to 3 – 4 monthly in stable responders
	Peripheral blood PCR	3 monthly initially, to assess molecular response, then 3 - 4 monthly in stable responders
	Bone marrow cytogenetics	annually until CCR and MMR achieved, and thereafter if concerns or loss of molecular response
	LFTs & U&Es	monthly initially, then every 3 – 6 months
	Serum lipase	every 2 weeks for the first 2 months, then every 3–6 months
	Blood pressure	baseline, and as indicated (see Comments)

Comments: Ponatinib is associated with serious arterial and venous vascular occlusive events.
The following is advised for all patients:

- 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.
- Hypertension should be medically controlled during ponatinib treatment, interruption of which should be considered if hypertension is not controlled.
- Patients should be monitored for evidence of vascular occlusion or thromboembolism, and treatment should be interrupted immediately if this occurs.

Reason for Update: Hep B statement added; indications updated; hepatotoxicity table added	Approved by Chair of Alliance TSSG: Dr A Laurie
Version: 3	Date: 4.9.17
Supersedes: Version 2	Review date: September 2020
Prepared by: S Taylor	Checked by: C Tucker

Interactions: Ponatinib is a substrate of CYP3A4. Therefore, concomitant use of strong inducers of CYP3A4 (e.g. phenytoin, carbamazepine, rifampicin, St Johns wort) and ponatinib should be avoided, as this may increase the risk of therapeutic failure.

The manufacturer advises that caution should be exercised and reduction of ponatinib starting dose to 30mg should be considered with concurrent use of ponatinib and strong CYP3A inhibitors (e.g. clarithromycin, itraconazole, posaconazole, voriconazole, telithromycin) as they may increase exposure to ponatinib.

Dose Modifications

Haematological Toxicity: If neutrophils < 1.0 x 10^9/L or platelets < 50 x 10^9/L, and not thought to be related to the leukaemia, withhold treatment until neutrophils ≥ 1.5 and platelets ≥ 75, then manage as follows:

First occurrence:	re-start at initial dose of 45mg daily
Second occurrence:	re-start at reduced dose of 30mg once daily
Third occurrence:	re-start at reduced dose of 15mg once daily

Pancreatitis:

Grade 2 asymptomatic pancreatitis or elevation of lipase/amylase	Continue at same dose
Grade 3 or 4 asymptomatic elevation of lipase/amylase only (> 2 x ULN)	*Occurrence at 45mg:* withhold ponatinib and resume at 30 mg after recovery to ≤ Grade 1 (< 1.5 x IULN) *Recurrence at 30 mg:* withhold ponatinib and resume at 15 mg after recovery to ≤ Grade 1 (< 1.5 x IULN) *Recurrence at 15 mg:* consider discontinuing ponatinib
Grade 3 pancreatitis	*Occurrence at 45mg:* withhold ponatinib and resume at 30 mg after recovery to < Grade 2 (asymptomatic, enzyme elevation only) *Recurrence at 30 mg:* withhold ponatinib and resume at 15 mg after recovery to < Grade 2. *Recurrence at 15 mg:* consider discontinuing ponatinib
Grade 4 pancreatitis	Discontinue ponatinib

Hepatotoxicity:

ALT/AST *either* > 3 – 5 × ULN for longer than 7 days *or* > 5 x ULN	*Occurrence at 45 mg:* interrupt ponatinib and monitor LFTs, and resume at 30 mg after recovery to ≤ Grade 1 (< 3×ULN), or has returned to pre-treatment grade *Occurrence at 30 mg:* interrupt ponatinib and resume at 15 mg after recovery to ≤ Grade 1, or has returned to pre-treatment grade *Occurrence at 15 mg:* discontinue ponatinib
Elevation of AST or ALT ≥ 3×ULN *concurrent with* bilirubin > 2xULN and ALP < 2×ULN	Discontinue ponatinib

Other non-haem Toxicity: Withhold ponatinib in the event of a severe non-haematological adverse reaction. After the event is resolved or attenuated in severity, ponatiniib may be resumed at the same dose, or at a reduced dose, according to the grade of reaction.

Renal Impairment: Renal excretion is not a major route for elimination, so accumulation of ponatinib is not expected in renal impairment. However, it has not been studied in renal impairment and so should be used with caution in patients with CrCl < 50ml/min.

Hepatic Impairment: Patients with hepatic impairment may receive the recommended starting dose. Use with caution in patients with hepatic impairment.

Patient Information: Ponatinib leaflet available at cancerresearchuk.org

Reason for Update: Hep B statement added; indications updated; hepatotoxicity table added	Approved by Chair of Alliance TSSG: Dr A Laurie
Version: 3	Date: 4.9.17
Supersedes: Version 2	Review date: September 2020
Prepared by: S Taylor	Checked by: C Tucker