

Chemotherapy Protocol

Chronic Myeloid Leukaemia

Ponatinib

All licensed indications are not funded therefore an application for funding is required before prescribing ponatinib.

Regimen

- Ponatinib

Indication

- As an option for the treatment of patients with chronic, accelerated or blast phase chronic myeloid leukaemia (CML) who are resistant and / or intolerant to other tyrosine kinase inhibitors
- As an option for the treatment of patients with chronic, accelerated or blast phase CML with T315I mutation.

Toxicity

Drug	Adverse Effect
Ponatinib	Arterial and venous thrombosis/occlusion, upper respiratory tract infection, pneumonia, hypothyroidism, insomnia, headaches, dizziness, visual disturbance, myocardial infarction, atrial fibrillation, cardiac failure, pericardial effusion, hypertension, dyspnoea, cough, gastrointestinal disturbance, pancreatitis, lipase elevations, LFT elevations, rash, bone pain, peripheral oedema.

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

- FBC, U&Es and LFTS every two weeks for the first three months, then monthly thereafter or as clinically indicated.
- Serum lipase or amylase every two weeks for the first two months, then periodically thereafter (acute pancreatitis occurs more frequently in the first two months of therapy).
- Hepatitis B, C and HIV status should be checked prior to starting ponatinib therapy. Patients who are carriers of HBV and those with active disease should be discussed with a consultant hepatologist prior to starting ponatinib therapy.

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and drug specific toxicities only. Dose adjustments may be necessary for other toxicities as well.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.

Haematological

Dose modifications for haematological toxicity in the table below are for general guidance only. Always refer to the responsible consultant as any dose reductions or delays will be dependent on clinical circumstances and treatment intent.

Consider blood transfusion or the use of erythropoietin according to NICE TA323 if patient symptomatic of anaemia or where the haemoglobin is less than 8g/dL.

Neutrophils (x10 ⁹ /L)	Dose Modifications
Less than 1	<ol style="list-style-type: none"> 1. Withhold ponatinib and monitor full blood count. 2. Once neutrophils have recovered to greater than or equal to 1.5x10⁹/L then resume ponatinib at a dose of 45mg (1st occurrence), 30mg (2nd occurrence) or 15mg (3rd occurrence) 3. After the 4th occurrence consider stopping ponatinib.
Platelets (x10 ⁹ /L)	Dose Modifications
Less than 50	<ol style="list-style-type: none"> 1. Withhold ponatinib and monitor full blood count. 2. Once platelets have recovered to greater than or equal to 75x10⁹/L resume the ponatinib at a dose of 45mg (1st occurrence), 30mg (2nd occurrence) or 15mg (3rd occurrence) 3. After the 4th occurrence consider stopping ponatinib.

Hepatic Impairment

Patients with hepatic impairment can safely receive the starting dose of ponatinib. The following are dose recommendations for those patients experiencing elevations of ALT/AST during ponatinib therapy.

Drug	Bilirubin μ mol/L		AST/ALT units	Dose (% of original dose)
Ponatinib	-		Grade 3 (more than 5xULN) or Grade 2 (more than 3xULN – 5xULN) for more than 7 days	<ol style="list-style-type: none"> 1. Stop ponatinib and monitor LFTs 2. Once AST/ALT has recovered to less than or equal to 3xULN (Grade 1 or better) then resume ponatinib at a reduced dose of 30mg if previously taking 45mg or 15mg if previously taking 30mg. 3. If previously taking 15mg consider stopping ponatinib treatment.
	Greater than 2xULN	and	Greater than or equal to 3xULN	Stop ponatinib

Renal Impairment

Renal excretion is not a major route of elimination. Patients with estimated creatinine clearance of greater than or equal to 50mL/min can start ponatinib with no dosage adjustment. However, caution is advised when administering ponatinib to patients with a creatinine clearance of less than 50mL/min, or end-stage renal disease as ponatinib has not been studied in this patient cohort.

Pancreatitis

	Dose modification
Grade 2 pancreatitis and/or asymptomatic elevations of serum lipase/amylase	Continue ponatinib at the same dose
Greater than 2xULN asymptomatic elevations of serum lipase/amylase	<p>Occurrence at 45mg:</p> <ul style="list-style-type: none"> Withhold ponatinib and resume at 30mg after recovery to less than or equal to grade 1 (less than 1.5xULN) <p>Recurrence at 30mg:</p> <ul style="list-style-type: none"> Withhold ponatinib and resume at 15mg after recovery to less than or equal to grade 1 (less than 1.5xULN) <p>Recurrence at 15 mg:</p> <ul style="list-style-type: none"> Consider discontinuing ponatinib
Grade 3 pancreatitis	<p>Occurrence at 45 mg:</p> <ul style="list-style-type: none"> Withhold ponatinib and resume at 30mg after recovery to < Grade 2 <p>Recurrence at 30mg:</p> <ul style="list-style-type: none"> Withhold ponatinib and resume at 15mg after recovery to less than grade 2 <p>Recurrence at 15mg:</p> <ul style="list-style-type: none"> Consider discontinuing ponatinib
Grade 4 pancreatitis	Discontinue ponatinib

Regimen

28 day cycle until disease progression or intolerance (12 cycles will be set in Aria)

Drug	Dose	Days	Administration
Ponatinib	45mg once a day	1-28 (inclusive)	Oral

Dose Information

- Ponatinib is available as 15mg and 45mg film-coated tablets.

Administration Information

- Ponatinib should be swallowed whole, either with or without food. The film-coated tablets should not be crushed or dissolved prior to administration.
- Ponatinib can cause drowsiness. If this happens, do not drive or use tools or machinery.

Additional Information

- The National Patient Safety Alert on oral chemotherapy (NPSA/2008/RRR001) must be followed in relation to ponatinib.
- It must be made clear to all staff, including those in the community, that ponatinib should only be prescribed under the supervision of a consultant haematologist.
- Ponatinib interacts with many other agents. Always check for drug interactions.

Coding

- Procurement – X71.5
- Delivery – X73.1

References

1. Ariad Pharma (UK) Limited (2016). Iclusig 15mg and 45mg film-coated tablets Summary of Product Characteristics. Electronic Medicines Compendium. Online at <http://www.medicines.org.uk/emc/medicine/28145>, accessed 4 October 2016.
2. Cortes, JE., Kim, D-W., Pinilla-Ibarz, J., le Coutre, P. and Paquette, R., et al. A Phase 2 Trial of Ponatinib in Philadelphia Chromosome-Positive Leukemias. *N Engl J Med* 2013; **369**(19):1783-96.

REGIMEN SUMMARY

Ponatinib

Cycle 1 onwards

Day 1-28

1. Ponatinib 45mg once a day oral

Administration Information
Oral chemotherapy

Swallow whole, do not crush or chew. This medicine may make you sleepy. If this happens do not drive or use tools or machinery.

Please supply the nearest original pack size according to local practice eg 30 tablets per 28 day cycle

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	January 2017	None	Eleanor Taylor Pharmacist	Dr Andrew Duncombe Consultant Haematologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors that occur as a result of following these guidelines.