Ponatinib

Indication
Chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia (CML) in patients who have the T315I mutation.
Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) in patients who have the T315I mutation.

ICD-10 codes
C92.1, C91.0

Regimen details

Day	Drug	Dose	Route
1-28 (continuously)	Ponatinib	45mg OD	PO

Cycle frequency
Continuous as above.

Number of cycles
As above, continued until disease progression or unacceptable toxicity. Patients should be reviewed and treatment discontinued if a complete haematological response has not occurred by 3 months.

Administration
Ponatinib is available as 15mg and 45mg tablets. Tablets should be swallowed whole, with or without food. The dose should be taken at the same time each day.

Patients should be advised to avoid grapefruit and grapefruit juice.

This product contains lactose monohydrate and it should not be used for patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

Pre-medication
Adequate hydration and allopurinol to prevent occurrence of tumour lysis syndrome should be considered.

Emetogenicity
This regimen has low emetic potential.

Additional supportive medication
Antiemetics as per local policy if required.
Allopurinol 300mg OD (100mg OD if CrCl < 20mL/min) for the first cycle (4 weeks) if required for tumour lysis syndrome.

Extravasation
N/A

Investigations – pre first cycle

Investigation	Validity period
FBC	7 days
Coagulation screen	7 days
U+Es (including creatinine)	7 days
LFTs	7 days
Blood pressure	7 days
Serum lipase	7 days

Confirmation of T3151 mutation.
Hepatitis B (HBV) serology testing – cases of reactivation of HBV have occurred in patients who are chronic carriers of HBV after they received BCR-ABL tyrosine kinase inhibitors.

Before starting treatment with ponatinib, the cardiovascular status of the patient should be assessed from the clinical and past medical history. Cardiovascular risk factors should be actively managed. Cardiovascular status should continue to be monitored and therapy optimised during treatment with ponatinib. Ponatinib should not be used in patients with a history of myocardial infarction or stroke, unless the potential benefit of treatment is considered to outweigh the potential harm.

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	Two weekly for the first 3 months, then monthly
U+Es (including creatinine)	Monthly
LFTs	Monthly
Serum lipase	Two weekly for the first 3 months, then monthly
Blood pressure	Monthly for the first 3 months then as clinically indicated

Marrow assessment (karyotype, FISH), peripheral blood BCR-ABL1/ABL1 or relevant marker for disease monitoring.

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 50 x 10^9/L
CrCl	≥ 50 mL/min
Serum lipase	< 2 x ULN
Bilirubin	< 2x ULN
AST/ALT	< 3 x ULN

Dose modifications

- **Haematological toxicity**

If neutrophils < 1.0 x 10^9/L and/or platelets < 50 x 10^9/L, and not thought to be disease related:
-First occurrence: Withhold treatment until neutrophils ≥ 1.5 x 10^9/L and platelets ≥ 75 x 10^9/L, then recommence at 45mg OD.
-Second occurrence: Withhold treatment until neutrophils ≥ 1.5 x 10^9/L and platelets ≥ 75 x 10^9/L, then recommence at 30mg OD.
-Third occurrence: Withhold treatment until neutrophils ≥ 1.5 x 10^9/L and platelets ≥ 75 x 10^9/L, then recommence at 15mg OD.

- **Renal impairment**

Renal excretion is not a major route of ponatinib elimination but ponatinib has not been studied in patients with renal impairment. For patients with calculated creatinine clearance of ≥ 50 mL/min no dosage adjustment is advised. Use with caution if estimated creatinine clearance < 50 mL/min.

- **Hepatic impairment**

Ponatinib is primarily eliminated via hepatic metabolism.
Patients with hepatic impairment may receive the recommended starting dose, however caution is advised.
Ponatinib may cause elevation in ALT, AST, bilirubin, and alkaline phosphatase; dose modification or interruption may be required. Liver function tests should be monitored as above or as clinically indicated.

AST /ALT (x ULN)		**Bilirubin** (x ULN)	**Ponatinib dose**
> 3	and	< 2	Withhold ponatinib and monitor LFTs Resume at 30mg dose on recovery (< 3 x ULN) If occurs at 30mg dose, withhold and resume at 15mg dose on recovery. If occurs at 15mg dose – discontinue.
> 3	and	> 2	Discontinue

- **Other toxicities**

Pancreatitis

Toxicity	**Definition**	**Dose adjustment**
Elevated lipase / amylase – asymptomatic	Grade 2 and asymptomatic	100% dose
	Grade 3-4 (> 2 x ULN) and asymptomatic	1st occurrence: withhold ponatinib and recommence at 30mg dose when ≤ grade 1 (<1.5 x ULN)
		2nd occurrence: withhold ponatinib and recommence at 15mg dose when ≤ grade 1
		3rd occurrence: withhold ponatinib and consider discontinuing treatment.
Pancreatitis – symptomatic	Grade 3	1st occurrence: withhold ponatinib and recommence at 30mg dose when < grade 2 (asymptomatic enzyme elevation)
		2nd occurrence: withhold ponatinib and recommence at 15mg dose when < grade 2
		3rd occurrence: withhold ponatinib and consider discontinuing treatment.
	Grade 4	Discontinue treatment

Arterial or venous thrombosis
Stop ponatinib and treat thrombosis. A benefit-risk consideration should guide any decision to restart therapy.

Hypertension
During treatment, blood pressure should be closely monitored (as clinically indicated). Hypertension should be treated and managed. Ponatinib treatment should be temporarily interrupted if hypertension is not medically controlled.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Arterial and venous thrombosis, including myocardial infarction, stroke
Congestive heart failure
Haemorrhage
Pancreatitis

- **Commonly occurring side effects**

Myelosuppression
Deranged liver function
Headache
Dizziness
Diarrhoea
Nausea and vomiting
Abdominal pain
Hypertension
Arthralgia, myalgia

- **Other side effects**

Cough, dyspnoea
Rash, dry skin
Fatigue
Reduced appetite

Significant drug interactions – for full details consult product literature/ reference texts

Potent/moderate CYP3A4 inhibitors (including ketoconazole, itraconazole, voriconazole, ritonavir, clarithromycin, and telithromycin) avoid concomitant treatment (or reduce starting dose to 30mg OD) – increases ponatinib exposure.

CYP3A4 inducers (including dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital and St John's Wort) avoid concomitant use - may induce ponatinib metabolism, potentially increasing the risk of therapeutic failure.

Anticoagulants: use with caution in patients at risk of bleeding events.

Caution should be used if ponatinib is administered with substrates of P-gp (e.g., digoxin, dabigatran, colchicine, pravastatin) or BCRP (e.g., methotrexate, rosuvastatin, sulfasalazine). Ponatinib may increase the plasma concentration of these agents.

In studies no clinically significant QT prolongation was observed. However, a thorough QT study has not been performed; therefore a clinically significant effect on QT cannot be excluded.

Additional comments

Ponatinib is associated with vascular occlusive events, including cardiovascular; cerebrovascular; and peripheral vascular adverse events, and venous thrombotic 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.

Women of childbearing potential and men must be advised to use effective contraception during treatment.

References

- European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Baccarani M, Deininger MW et al . Blood. 2013 Aug 8;122(6):872-84. doi: 10.1182/blood-2013-05-501569
- Summary of Product Characteristics Ponatinib (Ariad), accessed 29 April 2015 via http://www.medicines.org.uk – updated with SPC update 26/10/16

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