Thames Valley
Strategic Clinical Network

PONATINIB

INDICATION

Licensed / NICE TA 451 (BLUETEQ required)

Treatment of chronic, accelerated or blast phase Chronic Myeloid Leukaemia (CML) if

- the disease is resistant to dasatinib or nilotinib, or
- the patient cannot have dasatinib or nilotinib and subsequent treatment with imatinib is not clinically appropriate, or
- T315I gene mutation is present

Treatment of Philadelphia chromosome positive Acute Lymphoblastic Leukaemia (ALL) if

- subsequent treatment with imatinib is not clinically appropriate, or
- T315I gene mutation is present

Available as 15mg, 30mg and 45mg tablets

TREATMENT INTENT

Disease modification

PRE-ASSESSMENT

1. Investigations to include FBC, blood film and manual differential, coagulation screen, urea and electrolytes, liver function tests, bone profile, lipid profile, fasting glucose or HbA1c, BNP, amylase, urate, CK, HIV, Hepatitis B (including HB surface Ag and HB core antibodies) and C testing.
2. Ensure diagnosis is confirmed prior to commencing treatment (usually PCR on peripheral blood and bone marrow aspirate morphology with FISH for Ph chromosome). Results of full karyotype are important to exclude major route abnormality (extra Philadelphia (Ph) chromosome, trisomy 8, isochromosome 17q or trisomy 19) but treatment can be commenced prior to the karyotype becoming available. For second line treatment for resistance, it is recommended to carry out bone marrow, cytogenetics and kinase domain mutation screen testing prior to switch of treatment.
3. Pregnancy Test - for all women of childbearing age unless they are postmenopausal or have undergone a hysterectomy.
4. Record performance status (WHO/ECOG).
5. Record height and weight.
6. Record blood pressure
7. ECG (most TKIs can affect the QT interval)
8. Consider echocardiogram in selected patients at risk of cardiac disease
9. ELTS or SOKAL risk score should be documented at diagnosis for all CML patients (LINK)
10. QRISK3 score (LINK - some TKIs have been associated with increased risk of cardiovascular disease and vascular risk factors should be considered and managed as appropriate)

11. Record pedal pulses in clinical notes and consider referral to primary care for ankle brachial pressure index test at baseline as ponatinib enhances the risk of arterial occlusion.
12. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given. Obtain written consent on the day of treatment.
13. Fertility - it is very important the patient understands the potential risk of infertility, all patients should be offered fertility advice (see fertility guidelines). Consider sperm storage/ cryopreservation in appropriate patients.
14. Treatment should be agreed in the relevant MDT.
15. Ensure pre-treatment counselling in line with national recommendations for oral systemic anti-cancer therapy (SACT).

DRUG REGIMEN / CYCLE FREQUENCY

Chronic Myeloid Leukaemia (CML)

PONATINIB 45mg PO once daily. Consider 30mg starting dose for chronic phase.

Acute Lymphoblastic Leukaemia (ALL)

PONATINIB 45mg PO once daily.

Continue until disease progression or unacceptable toxicity.

Consider discontinuing treatment if a complete haematologic response has not occurred by 3 months (90 days).

DOSE MODIFICATIONS

In patients that have achieved MMR, consider dose reduction to the minimum level to maintain molecular response to minimise risk of side effects. The risk of arterial occlusive events is likely to be dose-related. Reducing the dose of ponatinib to 15 mg should be considered for CP-CML patients who have achieved a major cytogenetic response taking the following factors into account in the individual patient assessment: cardiovascular risk, side effects of ponatinib therapy, time to response, and BCR-ABL transcript levels. Closely monitor response after dose reduction.

In the case of severe adverse reactions, withhold treatment.
For patients whose adverse reactions are resolved or attenuated in severity, Ponatinib may be restarted usually at a reduced dose, depending on the severity of the toxicity observed.

Vascular Occlusion

Careful risk assessment should be conducted in patients with a history of myocardial infarction, stroke and prior revascularisation before treatment.

In patients suspected of developing an arterial or venous occlusive event, stop Ponatinib. Consider benefit-risk before deciding to restart Ponatinib therapy after the event is resolved.
Hypertension may contribute to risk of arterial thrombotic events. Temporarily interrupt Ponatinib treatment if hypertension is not medically controlled.

Myelosuppression (unrelated to leukaemia)

ANC < 1.0 x 10^9/L or platelet < 50 x 10^9/L	**First occurrence** Withhold Ponatinib. 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. 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. Resume at 15mg after recovery to ANC ≥ 1.5 x 10^9/L and platelet ≥ 75 x 10^9/L

Pancreatitis & elevated Lipase / Amylase

Grade 2 pancreatitis and/or asymptomatic elevation of lipase/amylase	Continue Ponatinib at same dose
Grade 3 / 4 asymptomatic elevation of lipase/amylase (> 2 x ULN) only	**Occurrence at 45mg** Withhold Ponatinib. Resume at 30mg after recovery to ≤ Grade 1 (< 1.5 x ULN) **Recurrence at 30mg** Withhold Ponatinib. Resume at 15mg after recovery to ≤ Grade 1 (< 1.5 x ULN) **Recurrence at 15mg** Consider discontinuing Ponatinib
Grade 3 pancreatitis	**Occurrence at 45mg** Withhold Ponatinib. Resume at 30mg after recovery to < Grade 2 **Recurrence at 30mg** Withhold Ponatinib. Resume at 15mg after recovery to < Grade 2 **Recurrence at 15mg** Consider discontinuing Ponatinib
Grade 4 pancreatitis	Discontinue Ponatinib

Hepatotoxicity

Elevation of liver transaminase > 3 × ULN* Persistent grade 2 (longer than 7 days) Grade 3 or higher	**Occurrence at 45 mg:** Ponatinib should be interrupted and hepatic function should be monitored Ponatinib should be resumed at 30 mg after recovery to ≤ Grade 1 (< 3 × ULN), or recovery to pre-treatment grade **Recurrence at 30 mg:** Ponatinib should be interrupted and resumed at 15 mg after recovery to ≤ Grade 1, or recovery to pre-treatment grade **Recurrence at 15 mg:** Ponatinib should be discontinued
Elevation of AST or ALT ≥	Discontinue ponatinib

3 × ULN concurrent with an elevation of bilirubin > 2 × ULN and alkaline phosphatase < 2 × ULN	

Renal / Hepatic Impairment

Renal impairment	Hepatic impairment
No dose adjustment necessary. Caution is recommended in patients with CrCl < 50 mL/min	Patients with hepatic impairment may receive the recommended starting dose. Monitor closely and titrate to side effects/ response.

INVESTIGATIONS & ON-TREATMENT MONITORING

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Monitoring for Ponatinib		Frequency of Monitoring (Month 1)	Frequency of Monitoring (Month 2 and 3)	Frequency of Monitoring Once Stable
HIV, Hepatitis B and C serology	Baseline	N/A	N/A	N/A
Document Q-RISK score	Baseline	N/A	N/A	Annually
FBC	Baseline	1-2 weekly	Monthly	3 monthly
Biochemistry (U&Es, LFTs, bone profile)	Baseline	1-2 weekly	Monthly	3 monthly
BCR-ABL monitoring (for CML patients only)	Baseline	N/A	N/A	3 monthly *
Lipid profile	Baseline	N/A	N/A	Annually
BNP	Baseline	N/A	N/A	Annually
HbA1c	Baseline	N/A	N/A	Annually
TFTs	Baseline	N/A	N/A	Annually
Amylase	Baseline	Monthly	Monthly	As clinically indicated
Creatine kinase	Baseline	N/A	N/A	As clinically indicated
Blood pressure	Baseline	N/A	Monthly	3 monthly
Pedal pulses	Baseline	As clinically indicated	As clinically indicated	As clinically indicated
ECG	Baseline	At least 1 ECG following initiation	As clinically indicated	As clinically indicated
Echocardiogram & Chest X-ray #	As clinically indicated	N/A	As clinically indicated	As clinically indicated
ABL1 kinase domain mutation	At diagnosis	N/A	N/A	At warning or failure of response

* BCR-ABL monitoring every 3 months until the achievement of a stable MMR (<MR 3 – sustained for 1 year), and thereafter at 3-6 months as clinically indicated, as per BSH/ELN guidelines.

CXR should be performed in all patients who are SOB for assessment of pleural effusion Consideration should also be given to Echo in selected patients – for exclusion of pericardial effusion and assessment of left ventricular function as this can be affected by all TKIs.

CONCURRENT MEDICATION

Allopurinol 300mg OD for 14 days if not in CHR at time of starting ponatinib
Consider aspirin unless contra-indicated

CML patients only:
Consider GCSF support in patients with recurrent neutropenia.
Consider erythropoietin-stimulating agents (ESA) in anaemic patients.

EMETIC RISK

Low

DRUG INTERACTIONS

(Consult with pharmacist and refer to SPC for full details)

- Concomitant use of CYP3A4 inducers should be avoided (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or St John's Wort) as they may significantly reduce exposure to ponatinib, potentially increasing the risk of therapeutic failure.
- Caution should be taken when co-administering ponatinib, with strong CYP3A4 inhibitors (ketoconazole, itraconazole, voriconazole, erythromycin, clarithromycin), as they could increase ponatinib exposure. Consider reduction of the starting dose of ponatinib to 30mg if concurrent use cannot be avoided. Avoid grapefruit and grapefruit juice.
- Caution should be taken when co-administering ponatinib, with a CYP3A4 substrate with narrow therapeutic index (astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil or ergot analogues) as they could increase exposure to the CYP3A4 substrate.
- Ponatinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp (e.g., digoxin, dabigatran, colchicine, pravastatin) or BCRP (e.g., methotrexate, rosuvastatin, sulfasalazine) and may increase their therapeutic effect and adverse reactions. Close clinical surveillance is recommended when ponatinib is administered with these medicinal products.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

(Consult with pharmacist and refer to SPC for full details)

Pancreatitis, vascular occlusion, myelosuppression, upper respiratory tract infection, appetite decrease, insomnia, headache, dizziness, hypertension, dyspnoea, cough, abdominal pain, diarrhoea, vomiting, constipation, nausea, lipase increase, abnormal LFTs, rash, dry skin, bone pain, arthralgia, myalgia, pain in extremity, back pain, muscle spasms, fatigue, asthenia, peripheral oedema, pyrexia, pain, atrial fibrillation, myocardial infarction, anaemia, angina pectoris, thrombocytopenia, febrile neutropenia, congestive cardiac failure, cerebrovascular accident, sepsis, acute kidney injury, venous thrombotic reactions.

Patients should be counselled on monitoring using 4.4 of the SPC.

TKI should be discontinued 1 week before major surgery and restarted when risk of bleeding is considered to be minimal. Discuss with haematologist during surgery planning.

BCR -ABL tyrosine kinase inhibitors: risk of hepatitis B reactivation

- Test patients for infection with hepatitis B virus (HBV) before starting treatment with BCR-ABL tyrosine kinase inhibitors
- Consult experts in liver disease and in the treatment of HBV before starting treatment with BCR-ABL tyrosine kinase inhibitors in patients with positive HBV serology (including those with active disease) and for patients who test positive for HBV during treatment
- Patients who are carriers of HBV who require treatment with BCR-ABL tyrosine kinase inhibitors should be closely monitored for signs and symptoms of active HBV infection throughout treatment and for several months after stopping
- Suspected adverse drug reactions to BCR-ABL tyrosine kinase inhibitors should be reported via the Yellow Card scheme

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TREATMENT RELATED MORTALITY

Treatment related mortality is hard to estimate but patients should be consented for risk of death in view of considerable toxicity including vascular events and pancreatitis.

REFERENCES

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2. Incyte. Ponatinib Summary of Product Characteristics. Updated 28/7/2022.Accessed on 16/08/2023 via http://www.medicines.org.uk.
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4. Hochhaus et al (2017) Chronic Myeloid Leukaemia: ESMO Clinical Practice Guidelines. Ann Oncol 28(S4):iv41-51
5. Smith G et al (2020). A British Society of Haematology Guideline on the diagnosis and management of chronic myeloid leukaemia. B J Haem 191: 171-193
6. Hocchaus A et al (2020). European LeukemiaNet 2020 recommendations for treating chronic myeloid leukaemia. Leukemia 34: 966-984
7. Giraud, E.L. et al. (2023) 'Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: An update', The Lancet Oncology, 24(6). Doi:10.1016/s1470-2045(23)00216-4

REVIEW

Name	Revision	Date	Version	Review date
Julia Wong Pharmacist	New protocol	Mar 2017	1.0	
Cheuk-kie Cheung Pharmacist	General formatting	May 2017	1.1	
Cheuk-kie Cheung Pharmacist	Funding Update	Jul 2017	1.2, 1.3	
Cheuk-kie Jackie Cheung, Haematology Pharmacist. NSSG Myeloid Group	Annual protocol meeting	Oct 2019	1.4	Oct 2021
Dr Oni Chowdhury and Prof Adam Mead, Consultant Haematologists. Yen Lim, Zishaan Ramzan, Haematology Pharmacists. NSSG Myeloid Group.	Updated as per BSH/ELN guidelines and SPC. Addition of monitoring table, treatment-free period and reinitiation guidance. Annual protocol meeting 2022.	Aug 2023	2.0	Nov 2025