**Systemic Anti Cancer Therapy Protocol**

# Ponatinib
# Chronic Myeloid Leukaemia

**PROTOCOL REF: MPHAPONHA**
**(Version No: 1.0)**

## Approved for use in:

Treatment of chronic, accelerated or blast phase chronic myeloid leukaemia (CML) if one of the following is met **(NICE TA451)**:

- The disease is resistant to dasatinib or nilotinib
- The patient cannot have dasatinib or nilotinib and imatinib is not clinically appropriate
- T315I gene mutation is present

**Note that Blueteq registration <u>is required</u> for this indication**

## Dosage:

**Chronic, accelerated or blast phase CML**

| Drug | Dose | Route | Frequency |
|---|---|---|---|
| **Ponatinib** | **45mg** | PO | Daily continuous. |

**Consider 30mg daily starting dose for chronic phase**

## Administration:

- Ponatinib can be taken with or without food.
- Tablets should not be crushed, cut or chewed.
- Patients should be encouraged to report severe oedema early to their haematology team.

## Anti-emetic risk:

Mild/moderate or severely emetogenic.

Low Risk

## Supportive treatments:

Consider allopurinol 300mg once daily during first cycle

Consider aspirin unless contraindicated

## Dosing in renal and hepatic impairment:

| Renal | Hepatic |
|---|---|
| Use with caution | Patients with mild, moderate or severe hepatic impairment may receive the recommended starting dose, but used with caution |

## Interactions:

- Concomitant use of CYP3A4 inducers including dexamethasone, phenytoin, carbamazepine, rifampicin, and phenobarbital should be avoided as this may significantly reduce exposure to ponatinib.
- Concomitant use of CYP3A4 inhibitors including ketoconazole, itraconazole, voriconazole, erythromycin and clarithromycin should be avoided as this may significantly increase exposure to ponatinib.
- Caution should be taken when co-administrating ponatinib with substrates of CYP3A4 with a narrow therapeutic index astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil or ergot alkaloids as this can increase exposure to the CYP3A4 substrate.

**Inform GP and patient when starting treatment of interaction risk and to use caution when prescribing or taking other medications while on ponatinib.**

## Investigations and treatment plan:

| | Pre | Cycle 1 | Cycle 2 onwards | Ongoing |
|---|---|---|---|---|
| Informed Consent | X | | | |
| Clinical Assessment | X | X | X | Prior to every cycle |
| SACT Assessment (including toxicity assessment and PS) | | X | X | Prior to every cycle |
| ECHO and ECG | X | | | If clinically indicated. Note ponatinib can prolong the QTc |
| Chest X Ray | X | | | If clinically indicated |
| SOKAL | X | | | |
| QRISK3 | X | | | To guide suitability for ponatinib therapy |
| BCR-ABL PCR | X | X | X | PCR test can take a few days to process so results will be reviewed retrospectively |
| FBC | X | X | X | Prior to every cycle. A cycle may extend to three months in length once patients are stable on treatment. FBC should be taken within 7 days of prescribing but may be taken up to 14 days prior to prescription at clinician's discretion. **Prescribers must check FBC prior to prescribing and document that this check has taken place in the medical notes. SACT assessment will not include checking of this parameter in this instance.** |
| U&E & LFTs | X | X | X | Must have had within 6 months of prescription. **Prescribers must check U+E & LFT prior to prescribing and document that these checks have taken place in the medical notes. SACT assessment will not include checking of these parameters in this instance.** |
| Lipid profile | X | | | Repeat six monthly |
| B-type natriuretic peptide | X | | | Repeat yearly |
| Glucose and HbA1C | X | | | Repeat six monthly |
| Thyroid function tests | X | | | Repeat yearly |
| Amylase | X | | | Then as clinically indicated |
| Blood Pressure | X | X | X | Prior to each prescription |

| | | | | |
|---|---|---|---|---|
| Height | X | | | |
| Weight | X | X | X | Prior to every cycle |
| Ankle brachial pressure index test | X | | | Consider referral to vascular for this test at baseline if significant risk factors for peripheral vascular disease. |
| Pedal pulse | X | X | X | Prior to each prescription |
| Pregnancy test | X | | | If clinically indicated |
| Hepatitis B (including surface antigen and HB core antibody) and Hepatitis C testing | X | | | |

## Haematological toxicity:

| | | |
|---|---|---|
| All doses | ANC <1 x$10^9$<br><br>and/or<br><br>Platelets <50 x$10^9$ | 1. Stop treatment until ANC 1.5 x$10^9$/L and platelets ≥ 75 x$10^9$/L.<br>2. Resume treatment at the original starting dose.<br>3. If recurrence of ANC < 1 x$10^9$/L or, platelets <50 x$10^9$, repeat step 1 and resume treatment at a reduced dose of **30mg daily** (second episode) or to **15mg daily** (third episode). |

## Dose Modifications and Toxicity Management:

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

*Vascular Occlusion*

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.

*Side effects*

**Common**: Pancreatitis, vascular occlusion, myelosuppression, upper respiratory tract infection, appetite decrease, insomnia, headache, dizziness, hypertension, dyspnoea, cough, abdominal pain, diarrhoea, vomiting, constipation, nausea, lipase increase, ALT/ AST increase, rash, dry skin, bone pain, arthralgia, myalgia, pain in extremity, back pain, muscle spasms, fatigue, asthenia, peripheral oedema, pyrexia, pain.

TKIs should be discontinued 1 week before major surgery and restarted when risk of bleeding is considered to be minimal.

**Please refer to the relevant SPC for more information on toxicities.**

## References:


1. NICE (2017) TA451. https://www.nice.org.uk/guidance/ta451 Accessed 31/01/2020.
2. Incyte. Iclusig 45mg film-coated tablets (Ponatinib). Summary of Product Characteristics. Updated 13/08/2019. Accessed on 31/01/2020
3. MHRA (2016) Drug Safety Update: BCR-ABL tyrosine kinase inhibitors: risk of hepatitis B reactivation
4. Lancet Oncology (2019). Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Accessed on 31/01/2020