PONATinib Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*Reimbursement Status
Treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia (CML) who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib, nilotinib and bosutinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation	C92	00302a	CDS
Treatment of adult patients with Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.	C91	00302b	CDS

**If the reimbursement status is not defined [i], the indication has yet to be assessed through the formal HSE reimbursement process.*

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

PONATinib is taken orally, once daily and treatment is continued until disease progression or unacceptable toxicity develops

Drug	Dose	Route	Diluent & Rate	Cycle
PONATinib	45mg daily	PO	Continuous	Continuous
The tablets should be swallowed whole. Patients should not crush or dissolve the tablets. PONATinib may be taken with or without food				
PONATinib is available as 15mg and 45mg tablets				

ELIGIBILTY:

- Indications as above
- T3151 mutation proven by mutational analysis where applicable

EXCLUSIONS:

- Hypersensitivity to PONATinib or any of the excipients
- Lactation

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Haematologist working in the area of haematological malignancies or

TESTS:

Baseline tests:

- FBC, liver and renal profile
- Bone profile

- Amylase, glucose and cholesterol
- **Hepatitis B Reactivation:** All patients should be tested for both HBsAg and HBcoreAb.
  *See Adverse Effects/Regimen Specific Complications
- Cardiovascular assessment; to include Baseline BP , ECG, ECHO, BNP ABPI, Cardiovascular risk score.

*** Before starting treatment with PONATinib, the cardiovascular status of the patient should be assessed, including history and physical examination, and cardiovascular risk factors should be actively managed. Cardiovascular status should continue to be monitored and medical and supportive therapy for conditions that contribute to cardiovascular risk should be optimised during treatment with PONATinib**

- Blood pressure should be measured at baseline and again within days of starting therapy
- Urine for protein

Regular tests:

- FBC, liver and renal profile, bone, Amylase, glucose and cholesterol weekly for the first month and then monthly or as clinically indicated
- Regular cardiovascular clinical assessment at least 3 monthly . Annual Echocardiogram and cardiovascular risk score. All modifiable cardiac risk factors should be addressed. Aspirin should be considered in patients with cardiac risk factors.
- Blood pressure should be measured at each visit. PONATinib associated hypertension should be aggressively managed.
- Hyperlipidemia should be actively managed with statins. Aspirin should be considered in patients with cardiac risk factors.

Disease monitoring:
Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.
- Patient should be monitored for response according to standard clinical guidelines
- Consideration should be given to dose reduction of PONATinib when the desired response has been achieved.
- Consider discontinuing PONATinib if a complete haematological response has not occurred by 3 months.
- Dose modifications or interruption of dosing should be considered for the management of haematological and non-haematological toxicities, and in particular cardiovascular toxicities. In the case of severe adverse reactions, treatment should be withheld.
- For patients whose adverse reactions are resolved or attenuated in severity, PONATinib may be restarted and escalation of the dose back to the daily dose used prior to the adverse reaction may be considered if clinically appropriate

Haematological:

Table 1: Dose modification of PONATinib in haematological toxicity

ANC (x10^9/L)		Platelets (x10^9/L)	Dose
< 1.0	or	<50	**First occurrence** Withhold PONATinib and resume initial 45mg dose after recovery to ANC ≥ 1.5 x 10^9/L and platelet ≥ 75 x 10^9/L
			Second occurrence Withhold PONATinib and resume at 30mg dose after recovery to ANC ≥1.5 x 10^9/L and platelet ≥75 x 10^9/L
			Third occurrence Withhold PONATinib and resume at 15mg dose after recovery to ANC ≥1.5 x 10^9/L and platelet ≥75 x 10^9/L

Renal and Hepatic Impairment:

Table 2: Dose modification of PONATinib in renal and hepatic impairment

Renal Impairment	Hepatic Impairment
• Renal excretion is not a major route of PONATinib elimination. PONATinib has not been studied in patients with renal impairment. Patients with estimated creatinine clearance of ≥ 50 mL/min should be able to safely receive PONATinib with no dosage adjustment. • Caution is recommended when administering PONATinib to patients with estimated creatinine clearance of < 50ml/min or end-stage renal disease.	• Patients with hepatic impairment may receive the recommended starting dose. • Caution is recommended when administering PONATinib to patients with severe hepatic impairment • See table 4 for dose modifications for hepatic toxicity

Management of adverse events:

Table 3: Dose Modification of PONATinib for Adverse Events

Adverse reactions	Recommended dose modification
Grade 2 pancreatitis and/or asymptomatic elevation of lipase/amylase	**Continue PONATinib at the same dose**
Grade 3 or 4 asymptomatic elevation of lipase/amylase (> 2.0 x ULN) only	**Occurrence at 45mg:** Withhold PONATinib and resume at 30mg after recovery to ≤ Grade 1 (< 1.5 x ULN) **Recurrence at 30mg:** Withhold PONATinib and 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 and resume at 30mg after recovery to < Grade 2 Occurrence at 30mg: Withhold PONATinib and resume at 15mg after recovery to < Grade 2 Occurrence at 15mg: Consider discontinuing PONATinib
Grade 4 pancreatitis	Discontinue PONATinib
Vascular occlusion	Interrupt treatment with PONATinib if patient suspected of developing an arterial or venous occlusive event. A benefit-risk consideration should guide a decision to restart PONATinib therapy after the event is resolved.

Table 4: Recommended dose modifications for hepatic toxicity

Elevation of liver transaminase >3 x ULN Persistent grade 2 (longer than 7 days) Grade ≥ 3	**Occurrence at 45mg:** • Interrupt PONATinib and monitor hepatic function • Resume PONATinib at 30mg after recovery to Grade ≤ 1 (< 3 x ULN), or has returned to pre-treatment grade. **Occurrence at 30mg:** • Interrupt PONATinib and resume at 15mg after recovery to ≤ Grade 1, or has returned to pre-treatment grade. **Occurrence at 15mg:** • Discontinue PONATinib.
Elevation of AST or ALT ≥ 3 x ULN concurrent with an elevation of bilirubin > 2 x ULN and alkaline phosphatase < 2 x ULN	Discontinue PONATinib

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Minimal (**Refer to local policy).**

PREMEDICATIONS:

None usually required

OTHER SUPPORTIVE CARE:

- Haematologic support such as platelet transfusion and haematopoietic growth factors can be used during

treatment if clinically indicated

- PONATinib has a minor influence on the ability to drive and use machines. Adverse reactions such as lethargy, dizziness, and vision blurred have been associated with PONATinib so caution should be recommended when driving or operating machines.
- Women of childbearing age being treated with PONATinib should be advised not to become pregnant and men being treated with PONATinib should be advised not to father a child during treatment. An effective method of contraception should be used during treatment. It is unknown whether PONATinib affects the effectiveness of systemic hormonal contraceptives. An alternative or additional method of contraception should be used.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

This medicinal product is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

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

- **Myelosuppression:** PONATinib is associated with severe grade 3 or 4 thrombocytopenia, neutropenia, and anaemia. The frequency of these events is greater in patients with accelerated phase CML (AP-CML) or blast phase CML (BP-CML)/Ph+ ALL than in chronic phase CML (CP-CML). A complete blood count should be performed every 2 weeks for the first 3 months and then monthly or as clinically indicated. Myelosuppression was generally reversible and usually managed by withholding PONATinib temporarily or reducing the dose
- **Vascular occlusion**: Arterial and venous thrombosis and occlusions, including fatal myocardial infarction, stroke, retinal vascular occlusions associated in some cases with permanent visual impairment or vision loss, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures have occurred in PONATinib treated patients. Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events. Vascular occlusion adverse events were more frequent with increasing age and in patients with prior history of ischaemia, hypertension, diabetes, or hyperlipidaemia.
  PONATinib should not be used in patients with a history of myocardial infarction, prior revascularization or stroke, unless the potential benefit of treatment outweighs the potential risk. In these patients, alternative treatment options should also be considered before starting treatment with PONATinib. Before starting treatment with PONATinib, the cardiovascular status of the patient should be assessed, including history and physical examination, and cardiovascular risk factors should be actively managed. Cardiovascular status should continue to be monitored and medical and supportive therapy for conditions that contribute to cardiovascular risk should be optimised during treatment with PONATinib. Monitoring for evidence of thromboembolism and vascular occlusion should be performed and if decreased vision or blurred vision occurs, an ophthalmic examination (including fundoscopy) should be performed. PONATinib should be interrupted immediately in case of vascular occlusion. A benefit -risk consideration should guide a decision to restart therapy.
- **Hypertension:** Hypertension may contribute to risk of arterial thrombotic events. During PONATinib treatment, blood pressure should be monitored and managed at each clinic visit and hypertension should be treated to normal. PONATinib treatment should be temporarily interrupted if hypertension is not medically controlled. Treatment-emergent hypertension (including hypertensive crisis) occurred in PONATinib-treated patients. Patients may require urgent clinical intervention for hypertension associated with confusion, headache, chest pain, or shortness of breath.
- **Congestive heart failure*:*** Fatal and serious heart failure or left ventricular dysfunction occurred in Iclusig-treated patients, including events related to prior vascular occlusive events. Monitor patients for signs or symptoms consistent with heart failure and treat as clinically indicated, including interruption of PONATinib. Consider discontinuation of PONATinib in patients who develop serious heart failure
- **Hepatitis B reactivation**. If either test is positive, such patients should be treated with lamivudine 100 mg/day

orally, for the entire duration of treatment and for six months afterwards. Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA at least every two months. If the hepatitis B virus DNA level rises during this monitoring, management should be reviewed with an appropriate specialist with experience managing hepatitis and consideration given to halting chemotherapy.

- **Pancreatitis and serum lipase:** PONATinib is associated with pancreatitis. The frequency of pancreatitis is greater in the first 2 months of use. Check serum lipase every 2 weeks for the first 2 months and then periodically thereafter. Dose interruption or reduction may be required. If lipase elevations are accompanied by abdominal symptoms, PONATinib should be withheld and patients evaluated for evidence of pancreatitis Caution is recommended in patients with a history of pancreatitis or alcohol abuse. Patients with severe or very severe hypertriglyceridemia should be appropriately managed to reduce the risk of pancreatitis.
- **Hepatotoxicity:** PONATinib may result in elevation in ALT, AST, bilirubin, and alkaline phosphatase. Hepatic failure (including fatal outcome) has been observed. Liver function tests should be performed prior to treatment initiation and monitored periodically, as clinically indicated**.**
- **Haemorrhage:** Serious bleeding events and haemorrhage, including fatalities, occurred in PONATinib-treated patients.

DRUG INTERACTIONS:

- Caution should be exercised with concurrent use of PONATinib and moderate and strong CYP3A inhibitors and moderate and strong CYP3A inducers.
- Concomitant use of PONATinib with anti-clotting agents should be approached with caution in patients who may be at risk of bleeding events. Formal studies of PONATinib with anti-clotting medicinal products have not been conducted.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

PONATinib - L01XE24

COMPANY SUPPORT RESOURCES/Useful Links:

Please note that this is for information only and does not constitute endorsement by the NCCP
HCP Brochure: https://www.hpra.ie/img/uploaded/swedocuments/d07ff31c-a064-4227-a42c-3f77a5e220f9.pdf

REFERENCES:

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2. Cortes JE, Kim DW, Pinilla-Ibarz J. et al . A Phase 2 Trial of PONATinib in Philadelphia Chromosome–Positive Leukemias. N Engl J Med, . (2013) 369, 1783-1796.
3. Moslehi JJ., Deininger M. Et al. Tyrosine Kinase Inhibitor-Associated Cardiovascular Toxicity in Chronic Myeloid Leukaemia. J Clin. Oncol., 2015:33;4210-4218.
4. Iclusig® Summary of product characteristics Accessed Nov 2018. Available at: https://www.ema.europa.eu/documents/product-information/iclusig-epar-product-information_en-0.pdf

Version	Date	Amendment	Approved By
1	20/12/2016		Dr Larry Bacon
2	15/01/2018	Updated to new NCCP template, Clarification of indication for CML	Dr Eibhlin Conneally/Dr Larry Bacon

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes
Further details on the Cancer Drug Management Programme is available at;
http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/