Drug Monograph

A - Drug Name

ponatinib

COMMON TRADE NAME(S): Iclusig®

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B - Mechanism of Action and Pharmacokinetics

Ponatinib is a potent BCR-ABL tyrosine kinase inhibitor that binds to native BCR-ABL and mutant forms, including T315I.

Absorption	Dose proportional increases in C_{max} and AUC between 15 to 60 mg.	
	Bioavailability	Absolute bioavailability unknown.
	Peak plasma levels	6 hours
Distribution	PPB	> 99%
Metabolism	Main enzymes involved	Esterases and/or amidases and by CYP3A4
	Active metabolites	No
	Inactive metabolites	Yes
Elimination	Feces	87%
	Urine	5%
	Half-life	22 hours

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C - Indications and Status

Health Canada Conditional Approvals
(pending the result of studies to verify the drug's clinical benefit. Patients should be advised of the nature of the marketing authorization granted.)

For the treatment of patients with chronic, accelerated or blast phase chronic myeloid leukemia (CML), or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) for whom other tyrosine kinase inhibitors (TKIs) are not appropriate, including patients who are T315I mutation positive, or where there is prior TKI resistance or intolerance.

Notes:

Conditional approval is based on improvement in response rate. No trials have demonstrated increased survival or improvement in symptoms.

Ponatinib is only prescribed and dispensed through a controlled distribution program. For more information, call 1-855-552-7423 or visit www.iclusigcdp.ca.

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D - Adverse Effects

Emetogenic Potential: Minimal – No routine prophylaxis; PRN recommended

Extravasation Potential: Not applicable

The following adverse effects were reported mainly in chronic phase CML patients or in pooled safety analyses.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (3%) (atrial fibrillation)	E
	Arterial thromboembolism (19%)	E
	Artery aneurysm (rare)	E D L
	Artery dissection (rare)	E D L
	Cardiotoxicity (8%) (cardiac failure)	E D

	Hypertension (17%)	E
	Pulmonary hypertension (2%)	E
	Venous thromboembolism (5%)	E
Dermatological	Alopecia (6%)	E
	Rash (40%) (may be severe)	E
	Skin discolouration (1%) (also hyperpigmentation)	E
Gastrointestinal	Abdominal pain (29%)	E
	Anorexia, weight loss (6%)	E
	Constipation (20%)	E
	Diarrhea (9%)	E
	Dry mouth (6%)	E
	Dyspepsia (3%) (also GERD)	E
	GI perforation (rare)	E
	Nausea, vomiting (15%)	I E
General	Fatigue (19%)	E
	Fever (9%)	E
	Fluid retention (including effusions) (28%) (1% severe)	E
Hematological	Myelosuppression ± infection, bleeding (35%) (grade 3 or 4)	E
Hepatobiliary	↑ Amylase / lipase (41%) (12% severe)	E
	↑ LFTs (18%) (4% severe)	E
	Pancreatitis (7%)	E
Immune	Other Atypical infections (including HBV reactivation)	D
Metabolic / Endocrine	Abnormal electrolyte(s) (severe: decreased Na 5%; increased K 2%)	E
	Hyperglycemia (7%) (severe)	E
	Hyperuricemia (7%)	E
	Hypothyroidism (rare)	D
	↓ PO4 (9%) (severe)	E
	Tumor lysis syndrome (<1%)	E
Musculoskeletal	Musculoskeletal pain (18%)	E
Nervous System	Dizziness (6%)	E
	Headache (24%)	E
	Insomnia (2%)	E
	Peripheral neuropathy (13%) (2% severe)	E

	RPLS / PRES (%) (rare)	E
Ophthalmic	Eye disorders (13%) (corneal irritation, dry eye, eye pain, blurred vision)	E
	Retinal vascular disorder (3%) (retinal vein occlusion, retinal hemorrhage)	E
Respiratory	Cough, dyspnea (7%)	E
Vascular	Hot flashes (3%)	E
	Peripheral ischemia (3%)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for ponatinib include myelosuppression ± infection, bleeding, rash, abdominal pain, headache, constipation, fatigue, musculoskeletal pain, hypertension, nausea, vomiting and ↑ amylase / lipase.

Arterial and venous thromboembolism and occlusions (including stroke, renal artery stenosis, peripheral vascular events, myocardial infarction, ocular, pulmonary embolism, mesenteric occlusions) occurred in 24% of patients with and without cardiovascular risk factors, some of which required revascularization procedures. The median onset of arterial occlusive events was 244 days, but may occur as early as two weeks. **Renal artery stenosis** has been reported and may be associated with worsening or treatment-resistant hypertension.

Vascular occlusive events were more frequent in older patients and those with a history of ischemia, hypertension, diabetes or hyperlipidemia. Peripheral vascular events sometimes required amputation. Before starting treatment, the cardiovascular status of the patient should be assessed and risk factors managed, with monitoring during treatment.

Severe cases of **artery dissection** (with or without hypertension) and **artery aneurysm** (including rupture) have been reported in patients using VEGFR TKIs.

Congestive heart failure and reduced left ventricular ejection fraction (LVEF) have been reported with an average onset of 196 days. LVEF should be evaluated prior to treatment. Symptomatic bradyarrhythmias and supraventricular tachyarrhythmias have been reported, with **atrial fibrillation** being the most common.

Severe **hemorrhage** (CNS, GI) occurred in 6% of patients with the incidence of this and severe neutropenia being higher in patients with acute or blast phase CML or Ph+ALL compared to chronic phase CML patients.

Hepatotoxicity that may be severe and life-threatening occurred within a week of starting treatment.

Pancreatitis was reported more frequently within the first two months of therapy.

Reactivation of hepatitis B virus (HBV) has been reported in patients who received BCR-ABL TKI's and are chronic carriers of HBV. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome. Patients should be tested for HBV infection prior to initiating treatment and an infectious disease specialist should be consulted. Carriers of HBV must be monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy.

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E - Dosing

- Ponatinib may only be prescribed and dispensed through a controlled distribution program.
- Patients' cardiovascular status should be assessed and risk factors managed prior to starting treatment and monitored during treatment.
- Ensure adequate hydration and correct hyperuricemia prior to starting treatment.

Adults:

Consider reducing the dose of ponatinib from 45 mg to 15 mg once daily for chronic phase CML patients who have achieved a MCyR (major cytogenetic response).

Consider discontinuation if a hematologic response has not been achieved by 3 months.

Oral: 45 mg Daily

Dosage with Toxicity:

Dose levels: 45 mg, 30 mg, 15 mg (if further dose reduction indicated, discontinue)

Doses reduced for toxicity may be re-escalated after toxicity has resolved, if clinically appropriate.

Toxicity	Severity	Action/ponatinib dose
Myelosuppression	ANC < 1 x 10^9/L or platelets < 50 x 10^9/L (unrelated to disease)	**1st occurrence:** Hold* until recovery, restart at the same dose. **2nd occurrence:** Hold* until recovery, restart at ↓ 1 dose level from previous dose.

		3rd occurrence: Hold* until recovery, restart at ↓ 1 dose level from previous dose.
Hemorrhage	Grade 3 or 4	Hold and investigate. Consider the risk vs. benefit of restarting.
LFTs	AST/ALT > 3 x ULN	Hold until recovery to ≤ grade 1, restart at ↓ 1 dose level from previous dose.
	AST/ALT ≥ 3 x ULN AND total bilirubin > 2 x ULN AND ALP < 2 x ULN	Discontinue`
Suspected Pancreatitis	Asymptomatic Amylase/lipase > 2 x ULN	Hold until recovery to ≤ grade 1 then restart at ↓1 dose level from previous dose.
	Amylase/Lipase elevations and symptomatic	Hold and investigate for pancreatitis.
	Grade 3 pancreatitis	Hold until recovery to < grade 2 then restart at ↓ 1 dose level from previous dose.
	Grade 4 pancreatitis	Discontinue
Hypertriglyceridemia	Grade 3 or 4	Manage patient appropriately to reduce pancreatitis risk.
Cardiac/ATE/VTE	Arterial or venous thromboembolic event	Discontinue unless benefit outweighs risk
	Blurred or decreased vision	Hold and refer for ophthalmic examination for suspected vascular occlusion. Consider the risk vs. benefit of restarting.
	LVEF < 50% and > 10% below baseline and asymptomatic	Hold until recovery. Discontinue if does not resolve within 4 weeks or is ≥ grade 3.
	Symptomatic CHF	Discontinue
	Arrhythmias	Hold and investigate.
	Hypertension	Treat to normalize blood pressure. Hold if not medically controlled and evaluate for renal artery stenosis.

Fluid retention		Hold, reduce or discontinue ponatinib as clinically indicated.
RPLS / PRES	Any	Hold if suspected Discontinue if confirmed or Restart if resolved and only if benefits outweigh risks
Other non-hematologic toxicity	Grade 3 or 4	Hold until recovery. Restart at ↓ 1 dose level from previous dose. If grade 4, consider discontinuation.
Major surgical procedures		Consider hold prior to surgery. Restart based on clinical judgement of adequate wound healing.
*Restart once ANC ≥ 1.5 x 10^9/L and platelets ≥ 75 x 10^9/L		

Dosage with Hepatic Impairment:

The recommended starting dose is 30 mg once daily in patients with hepatic impairment (Child-Pugh A, B or C). There was an increase in adverse effects in patients with severe hepatic impairment.

Dosage with Renal Impairment:

Renal excretion is not a major route of elimination. Dosage adjustment is not recommended, but ponatinib has not been studied in patients with CrCl < 50 ml/min or end-stage renal disease.

Dosage in the elderly:

Patients aged 65 and older were more likely to experience reduced efficacy and adverse effects compared to younger patients. The dose should be selected with caution given the greater frequency of decreased hepatic, renal and cardiac function, other diseases and drug therapies in older patients.

Children:

The safety and efficacy of ponatinib in patients under 18 years have not been established.

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F - Administration Guidelines

- Ponatinib should be swallowed whole with or without food
- Tablets should not be crushed, chewed or dissolved
- If a dose is missed, an additional dose should not be taken. Patients should take the next dose at the usual time.

Store at room temperature (15^{o}C to 30^{o}C) in the original package.

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G - Special Precautions

Contraindications:

- patients who have a hypersensitivity to this drug or any of its components
- patients who have uncontrolled hypertension or other unmanaged cardiac risk factors
- patients with a history of myocardial infarction, prior revascularization or stroke unless the potential benefit outweighs the risk
- patients with dehydration or untreated hyperuricemia

Other Warnings/Precautions:

- Consultation with a liver disease expert is recommended prior to starting ponatinib in chronic HBV carriers (including those with active disease), and for patients who test positive for HBV infection while on treatment
- patients aged 65 and older experienced reduced efficacy and increased adverse effects
- use with caution in patients with a prior history of ischemia, hypertension, congestive heart failure or conditions that may impair left ventricular function, diabetes or hyperlipidemia
- use with caution in patients with hepatic impairment
- use with caution in patients at risk of bleeding, those receiving antiplatelets and/or anticoagulants
- use with caution in patients with a history of pancreatitis or alcohol abuse

- contains lactose; carefully consider use in patients with hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption

Other Drug Properties:

- Carcinogenicity:
  Increased incidence of squamous cell carcinoma of the clitoral gland was observed in animals

Pregnancy and Lactation:

- Mutagenicity: No
- Clastogenicity: No
- Embryotoxicity: Yes
- Fetotoxicity: Yes
  Ponatinib is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least 6 months after the last dose. It is unknown whether ponatinib affects the effectiveness of oral contraceptives. An alternative method of contraception should be used.
- Excretion into breast milk: Unknown
  Breastfeeding is not recommended.
- Fertility effects: Likely

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H - Interactions

Ponatinib is metabolized by CYP3A4 and is therefore susceptible to drug interactions with inducers and inhibitors.

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP3A4 inhibitors (i.e. ketoconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges or starfruit)	↑ ponatinib concentration and/or toxicity (ketoconazole ↑ ponatinib exposure by 78%)	↓ metabolism of ponatinib	Caution. Consider reducing the starting dose of ponatinib to 30 mg with strong CYP3A4 inhibitors
CYP3A4 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc)	↓ ponatinib concentration and/or efficacy (rifampin ↓ ponatinib exposure by 62%)	↑ metabolism of ponatinib	Avoid strong CYP3A4 inducers if possible. If not possible, monitor for reduced efficacy of ponatinib

Drugs that raise gastric pH (e.g. proton pump inhibitors, H2-receptor antagonists, antacids)	co-admin with lansoprazole reduced Cmax without change in overall systemic exposure	higher pH results in lower solubility of ponatinib	No need to adjust dose or separate administration
P-glycoprotein substrates (i.e. verapamil, digoxin, morphine, ondansetron)	↑ substrate concentration and/or toxicity	ponatinib is an inhibitor of P-gp	Caution and monitor
BCRP substrates (i.e. topotecan, methotrexate, rosuvastatin)	↑ substrate concentration and/or toxicity	ponatinib is an inhibitor of BCRP	Caution and monitor

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Blood pressure	Baseline and as clinically indicated; ensure hypertension is controlled to minimize risk of arterial thromboembolism
CBC	Baseline, every 2 weeks for the first 3 months, and then monthly and as clinically indicated
Liver function tests	Baseline, at least monthly and as clinically indicated
Lipase, amylase	Baseline, every 2 weeks for the first 2 months, and then periodically or as clinically indicated
LVEF	Baseline, 3 months after treatment initiation, and as clinically indicated
Calcium, phosphate	Baseline and as clinically indicated

Eye exam and fundoscopy	Baseline, with blurred vision and as clinically indicated
HBV infection status	Prior to starting treatment and as clinically indicated during treatment; consult infectious disease if positive
For carriers of HBV: signs and symptoms of active HBV infection	At each visit during treatment and for several months after treatment discontinues
Clinical toxicity assessment for bleeding, infection, thromboembolism, fluid retention (including regular weight monitoring), hypertension, cardiac and GI effects, tumour lysis syndrome, ocular and neurologic effects	Baseline and at each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- ponatinib - For the treatment of Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia, according to specific clinical criteria
- ponatinib - For the treatment of Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL), according to specific clinical criteria

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K - References

BCR-ABL Tyrosine Kinase Inhibitors [GLEEVEC (imatinib mesylate), TASIGNA (nilotinib), BOSULIF (bosutinib), SPRYCEL (dasatinib), ICLUSIG (ponatinib hydrochloride)] - Risk of Hepatitis B Reactivation. Health Canada, May 4, 2016. [Accessed May 13, 2016]. Available from: http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2016/58222a-eng.php

Cortes JE, Kim DW, Pinilla-Ibarz J, et al; PACE Investigators. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. N Engl J Med. 2013 Nov 7;369(19):1783-96.

Iclusig product monograph. ARIAD Pharmaceuticals Inc. February 21, 2017.

Product Monograph Update: Vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR TKIs). Health Canada InfoWatch, June 2020.

September 2020 Updated adverse effects (artery aneurysm / dissection) based on Health Canada InfoWatch

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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