DRUG NAME: Ponatinib

SYNONYM(S): ponatinib hydrochloride, AP24534[1,2]

COMMON TRADE NAME(S): ICLUSIG®

CLASSIFICATION: miscellaneous

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Ponatinib is a tyrosine kinase inhibitor (TKI) with high-affinity against wild-type and mutant BCR-ABL kinase, as well as activity against vascular endothelial growth factor receptor, platelet-derived growth factor receptor, sarcoma kinases, fibroblast growth factor receptor, KIT (mast/stem cell growth factor receptor), ephrin, and RET (rearranged during transfection). Ponatinib is more potent *in vitro* than imatinib against wild-type BCR-ABL. Structurally, ponatinib contains a carbon-carbon triple bond to accommodate the T315I mutation, thus exhibiting anti-tumour activity against BCR-ABL mutant T315I cells.[1-6]

PHARMACOKINETICS:

Oral Absorption	time to peak: 6 h; pH dependent solubility	
Distribution	extensively distributed in the extravascular space	
	cross blood brain barrier?	no information found
	volume of distribution[1,2]	1101-1223 L
	plasma protein binding	>99%
Metabolism	mainly hepatic via CYP 3A4; also metabolized by esterases and/or amidases	
	active metabolite(s)	no information found
	inactive metabolite(s)	carboxylic acid and N-desmethyl metabolite
Excretion	mainly via feces	
	urine	5%
	feces	87%
	terminal half life[1,2]	22-24 h
	clearance[5]	35 L/h

Adapted from standard reference[1] unless specified otherwise.

USES:

Primary uses:

*Leukemia, chronic myelogenous

*Leukemia, acute lymphoblastic

Other uses:

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Caution:

- ***Vascular occlusion*** adverse events are reported; ponatinib is not recommended in patients with a history of myocardial infarction, prior revascularization or stroke. Hypertension may contribute to the risk of arterial thrombosis and occlusion events and should be well controlled prior to starting treatment.[1]
- ***Impaired wound healing*** has been associated with vascular endothelial growth factor (VEGF) inhibitors; hold ponatinib 7 days prior to surgery and re-initiate post-surgery based on clinical assessment of the wound site.[1,4]
- ***Ocular toxicities*** leading to blindness are reported; comprehensive eye exams prior to and during treatment are recommended.[1]
- ***Reactivation of Hepatitis B virus*** (HBV) has sometimes occurred in chronic carriers of HBV after receiving BCR-ABL tyrosine kinase inhibitors[7]; for recommended HBV screening and prophylaxis, see BC Cancer Protocol SCHBV ***Hepatitis B Virus Reactivation Prophylaxis.***[8]

Special populations: Elderly patients (65 years or older) are more likely to experience adverse reactions such as vascular occlusion, thrombocytopenia, peripheral edema, increased lipase, dyspnea, asthenia, decreased appetite, and muscle spasms.[1,4]

Carcinogenicity: no information found

Mutagenicity: Not mutagenic in Ames test. Ponatinib is not clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[1]

Fertility: No fertility studies have been conducted; however, degeneration of testes epithelium and follicular atresia with associated endometrial atrophy have been reported in animal studies.[1]

Pregnancy: Embryo-fetal toxicity (e.g., post-implantation loss, reduced fetal body weight, and multiple soft tissue and skeletal alterations) has been reported in animal studies. Women of childbearing potential and males should use contraception during treatment.[1]

Breastfeeding is not recommended due to the potential secretion into breast milk.

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[9]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (3-23%, severe 8-55%)[1-3]
	febrile neutropenia (1-25%, severe 1-60%)[1-3]
	leukopenia (severe 12-63%)
	lymphocytopenia (severe 10-37%)[2]
	neutropenia (severe 23-63%)[1,2]
	thrombocytopenia (severe 34-57%)[1,2]
cardiac	***atrial fibrillation*** (2-4%, severe 2%)[1,2]
	atrioventricular block (<1%)[2]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	bradycardia (1%, severe <1%)
	heart failure, including fatalities (2-15%, severe 1-8%)[1-3]; see paragraph following **Side Effects** table
	myocardial infarction (2-12%, severe <2%)[1,2]
	palpitations (2%)
	pericardial effusion (1-4%), severe 1-2%)[1,2]
	peripheral ischemia (8%)[2]
	sick sinus syndrome (<1%)[2]
	supraventricular tachycardia (5%)[2]
eye	blurred vision (3-6%)[1,2]
	conjunctivitis (1-2%, severe 1%)
	dry eyes (2-5% severe 1%)
	retinal toxicity (3%)[2], including macular edema, retinal vein occlusion, retinal hemorrhage; see paragraph following **Side Effects** table
gastrointestinal	*emetogenic potential:* low[10]
	abdominal pain (4-49%, severe 2-10%)[1-3]
	ascites (<1%)[2]
	constipation (5-47%, severe 1-3%)[1,2]
	diarrhea (2-26%, severe 1-3%)[1,2]
	dry mouth (1-6%)
	dyspepsia (1-3%)
	gastroesophageal reflux disease (2%)
	gastrointestinal hemorrhage (2-11%, severe ≤6%)[2]
	gastrointestinal fistula, perforation (<1%)[2]
	nausea (3-32%, severe 1-2%)[1-3]
	pancreatitis (5-8%, severe 3-6%); see paragraph following **Side Effects** table
	stomatitis (2-23%, severe 1-3%)[1-3]
	vomiting (3-24%, severe 1-2%)[1-3]
general disorders and administration site conditions	***asthenia/fatigue*** (6-39%, severe 1-6%)[1-4]
	chills (3-13%, severe 2%)[1,2]
	influenza-like illness (1-2%, severe 1%)
	pain (1-16%, severe 1-3%)[1,3]
	peripheral edema (5-22%; severe <1%)[1,2]
	pyrexia (3-32%, severe 1-5%)[1-3]
hepatobiliary	***acute hepatic failure*** (<1%)[2]; see paragraph following **Side Effects** table

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
infections and infestations	cellulitis (2-11%, severe <3%)[2,3]
	folliculitis (2-6%)
	nasopharyngitis (3-12%)[2]
	pneumonia (1-13%, severe 1-11%)[1-3]
	sepsis (1-22%; severe 1-22%)[2,3]
	upper respiratory tract infection (1-11%, severe <2%)[1-3]
	urinary tract infection (≤12%, severe 1%)[2,3]
investigations	***alkaline phosphatase increase*** (37%, severe 1-4%)[1,2]
	ALT increase (53%, severe 4-8%)[1,2]; see paragraph following **Side Effects** table
	amylase increase (3%, severe 1-5%)[1,3]
	AST increase (41%, severe 3-6%)[1,2]; see paragraph following **Side Effects** table
	bilirubin increase (19%, severe 1-3%)[1]
	creatinine increase (7%, severe <1%)[2,3]
	ejection fraction decrease (1-7%, severe 1-5%)
	gamma glutamyltransferase increase (3-9%, severe 2-4%)
	lipase increase (41%,severe 12-15%)[1]; see paragraph following **Side Effects** table
	weight decrease (2-13%, severe<1%)[1-3]
metabolism and nutrition	albumin decrease (28%, severe 1%)[2,3]
	appetite decrease (5-31%, severe 1%)[1,2]
	bicarbonate decrease (11%, severe <1%)[2,3]
	dehydration (1-6%, severe 1-3%)
	hypercalcemia (5%)[2]
	hyperglycemia (1-58%, severe 1-7%)[1,2]
	hyperkalemia (15%,severe 1-5%)[1,2]
	hypernatremia (10%, severe <1%)[2,3]
	hypertriglyceridemia (1-3%, severe <1%)
	hyperuricemia (1-7%, severe 1-3%)[1,2]; see paragraph following **Side Effects** table
	hypocalcemia (1-52%, severe 1-2%)[1,2]
	hypoglycemia (24%)[2]
	hypokalemia (1-16%, severe 1-5%)[1,2]
	hyponatremia (2-29%, severe 1-6%)[1,2]
	hypophosphatemia (3-57%, severe 3-12%)[1,2]
	tumour lysis syndrome (<1%)[2]; see paragraph following **Side Effects** table
	arthralgia (3-31%, severe 1-2%)[1,2]

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Clinically important side effects are in ***bold, italics***	
musculoskeletal and connective tissue	back pain (2-16%, severe <2%)[1-3]
	bone pain (3-12%, severe 1-3%)[1-3]
	limb pain (5-17%, severe <2%)[1-3]
	muscle spasms (2-13%)[1,2]
	myalgia (2-22%, severe 1%)[1,2]
nervous system	cerebral edema (<1%)[2]
	cerebral vascular accident (1-2%, severe 1%)[1,2]
	dizziness (1-11%, severe <1%)[1,3]
	dysgeusia (1-3%)
	headache (11-39%, severe 2-3%)[1-3]
	paraesthesia (1%)
	peripheral neuropathy (1-16%, severe 1-2%)[1-3]
psychiatric	confusion (1-6%, severe <1%)
	insomnia (2-12%)[1,2]
reproductive system and breast disorders	erectile dysfunction (4-6%)
respiratory, thoracic and mediastinal	cough (2-18%)[1,2]
	dysphonia (3%)
	dyspnea (6-21%, severe 2-7%)[1-3]
	epistaxis (2-5%, severe 2%)
	pleural effusion (2-19%, severe ≤3%)[1,2]
	pulmonary hypertension (2-3%, severe 1%)
skin and subcutaneous tissue	alopecia (5-7%)
	dermatitis exfoliative (1-7%, severe 2%)
	dry skin (18-40%, severe 1-3%)
	ecchymosis (1-3%)
	erythema (5-9%, severe 1%)
	hyperhidrosis (2-4%)
	hyperkeratosis (1-4%, severe <1%)
	petechiae (1-2%)
	periorbital edema (1-9%)
	pruritis (2-9%, severe 2%)
	rash (19-54%, severe 3-8%)[1-3]
	skin hyperpigmentation (1-2%)
vascular	***arterial ischemia*** (3-20%, severe ≤11%)[2]; see paragraph following **Side Effects** table

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	flushing (2%)
	hemorrhage (24%)[2]; see paragraph following **Side Effects** table
	hot flashes (3-4%)
	hypertension (2-71%, severe 3-39%)[1-3]; see paragraph following **Side Effects** table
	intermittent claudication (2%, severe 1%)
	peripheral arterial occlusive disease (3%, severe 2%); see paragraph following **Side Effects** table
	thromboembolic event (1-5%)[2,3]; see paragraph following **Side Effects** table

Adapted from standard reference[1] unless specified otherwise.

Heart failure and ***left ventricular dysfunction*** have been reported. Monitor patients for signs of heart failure and manage as clinically indicated. If new or worsening symptoms occur, interrupt or discontinue treatment. Permanently discontinue in patients who develop serious heart failure.[1,4]

Serious ***retinal toxicities***, including macular edema, retinal vein occlusion and retinal hemorrhage can occur and may lead to blindness. Ophthalmologic exams, including fundoscopy, are recommended at baseline and during treatment. Hold treatment if vascular occlusion is suspected; if diagnosis is confirmed, consider benefits and risks before restarting treatment.[1,4]

Elevated lipase and acute ***pancreatitis*** have been reported; frequency of pancreatitis is greater in the first two months of treatment. Patients with a history of pancreatitis or alcohol abuse may require more frequent monitoring. Hypertriglyceridemia, grade 3 or greater, should be managed to reduce the risk of pancreatitis. If patients develop elevated lipase with abdominal symptoms, interrupt treatment until a diagnosis of pancreatitis is ruled out. Dose interruption, reduction or discontinuation may be necessary. Most cases of pancreatitis resolve within 2 weeks of dose interruption or reduction. Discontinue treatment for grade 4 pancreatitis.[1,2,4]

Transaminase elevation and ***hepatic impairment*** can occur; transaminase elevations may be irreversible. Hepatotoxicity, including acute hepatic failure, has occurred within one week of starting treatment. Patients with hepatic impairment may also experience an increased incidence of adverse reactions. Monitor hepatic function prior to and during treatment. Dose interruption, reduction or discontinuation may be necessary. [1-3]

Hyperuricemia may result from cell lysis by ponatinib and may lead to electrolyte disturbances or acute renal failure.[11] It is most likely with highly proliferative tumours of massive burden, such as leukemias, high-grade lymphomas, and myeloproliferative diseases. The risk may be increased in patients with preexisting renal dysfunction, especially ureteral obstruction. Suggested prophylactic treatment for high-risk patients[12]:

- aggressive hydration: 3 L/m^2/24 hr with target urine output>100 mL/h
- if possible, discontinue drugs that cause hyperuricemia(e.g., thiazide diuretics) or acidic urine (e.g., salicylates)
- monitor electrolytes, calcium, phosphate, renal function, LDH, and uric acid q6h x 24-48 hours
- replace electrolytes as required
- allopurinol 600 mg PO initially, then 300 mg PO q6h x 6 doses, then 300 mg PO daily x 5-7 days

Urine should be alkalinized only if the uric acid level is elevated, using sodium bicarbonate IV or PO titrated to maintain urine pH>7. Rasburicase (FASTURTEC®) is a novel uricolytic agent that catalyzes the oxidation of uric acid to a water-soluble metabolite, removing the need for alkalinization of the urine.[13] It may be used for treatment or prophylaxis of hyperuricemia; however, its place in therapy has not yet been established. Aluminum hydroxide (e.g., AMPHOGEL®) may be added orally if phosphate becomes elevated. If aluminum hydroxide has been added, discontinue sodium bicarbonate.[14]

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Serious ***hemorrhagic events*** (e.g., hemorrhagic cerebral infarction, hemorrhagic gastritis) have been reported. Monitor blood counts regularly; dose interruption or reduction may be necessary.[1,4]

Hypertension, including hypertensive crisis, can occur with ponatinib. Monitor for hypertension and treat as clinically indicated. If hypertension cannot be controlled, dose interruption, reduction, or discontinuation may be necessary.[1,4]

Vascular occlusive events (e.g., arterial and venous thrombosis and occlusion) have been reported in 24% of patients, including in patients without cardiovascular risk factors and less than 50 years of age. Some serious arterial thrombosis and occlusions, including fatal myocardial infarction, fatal cerebral infarction, stroke, and arterial stenosis have occurred within 2 weeks of starting treatment. Vascular occlusive events are more frequent with increased age (greater than 65 years), prior history of ischemia, hypertension, diabetes, or hyperlipidemia. Monitor for signs of thromboembolism and vascular occlusion; recurrent and multi-site vascular occlusion have been reported. Assess the risk of recurrent arterial or venous occlusions before resuming treatment. Dose modification, discontinuation, or revascularization procedures may be necessary.[1,3,4]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
grapefruit juice[1]	may increase plasma level of ponatinib	may inhibit CYP 3A4 metabolism of ponatinib in the intestinal wall	avoid grapefruit and grapefruit juice for duration of treatment with ponatinib
ketoconazole[1]	ponatinib AUC increased by 78% and C_{max} increased by 47%	inhibits CYP 3A4 metabolism of ponatinib	reduce starting dose to 30 mg; monitor for adverse effects
rifampin[1]	ponatinib AUC reduced by 62% and C_{max} reduced by 42%	induces CYP 3A4 metabolism of ponatinib	avoid concurrent use
lansoprozole[1,3]	ponatinib AUC reduced by 6% and C_{max} reduced by 25%	pH-dependent solubility	dose adjustment or dose separation is not required

Ponatinib is a substrate of CYP 3A4. Strong CYP 3A4 inhibitors may increase ponatinib concentration and drug toxicity; reduce starting dose to 30mg. Strong CYP 3A4 inducers may reduce ponatinib concentration; avoid concurrent use if possible.[1,3,4]

Ponatinib is an inhibitor of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) *in vitro*; clinical significance is unknown.[1]

SUPPLY AND STORAGE:

Oral: GMD Distribution Inc. (for ARIAD Pharmaceuticals) supplies ponatinib hydrochloride as 15 mg film-coated tablets. Tablets contain lactose monohydrate and polyethylene glycol. Store at room temperature in original bottles.[1]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

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Adults:

BC Cancer usual dose noted in ***bold, italics***

Oral[1,15]*:*	***45 mg*** (range 15-45 mg) ***PO once daily.***
	Administer with food or on an empty stomach.
Concurrent radiation:	no information found
Dosage in myelosuppression:	modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"
Dosage in renal failure:	no information found
Dosage in hepatic failure[1]*:*	reduce starting dose to 30 mg PO once daily for any degree of hepatic impairment
Dosage in dialysis:	no information found

Children: no information found

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