Ponatinix

Ponatinib Hydrochloride INN

COMPOSITION

Ponatinix 15 Tablet: Each film coated tablet contains Ponatinib Hydrochloride INN equivalent to Ponatinib 15 mg.

Ponatinix 45 Tablet: Each film coated tablet contains Ponatinib Hydrochloride INN equivalent to Ponatinib 45 mg.

PHARMACOLOGICAL INFORMATION

Therapeutic Class: Anti-Cancer Agent

PHARMACOLOGICAL ACTION

Mechanism of Action:

Ponatinib is a kinase inhibitor. Ponatinib inhibited the in vitro tyrosine kinase activity of ABL and T315I mutant ABL with IC50 concentrations of 0.4 and 2.0 nM, respectively. Ponatinib inhibited the in vitro activity of additional kinases with IC50 concentrations between 0.1 and 20 nM, including members of the VEGFR, PDGFR, FGFR, EPH receptors and SRC families of kinases, and KIT, RET, TIE2, and FLT3. Ponatinib inhibited the in vitro viability of cells expressing native or mutant BCR-ABL, including T315I. In mice, treatment with Ponatinib reduced the size of tumors expressing native or T315I mutant BCR-ABL when compared to controls.

Pharmacodynamics:

In a cell-based assay, Ponatinib concentrations of 20 nM (10.65 ng/mL) were sufficient to suppress most BCR-ABL mutant clones. However, Ponatinib concentrations of 40 nM (21.3 ng/mL) were required to suppress T315I mutants. The median and range of steady-state Cmax and trough (Cmin) concentrations of Ponatinib following 29 days of once-daily dosing of 15 mg, 30 mg and 45 mg.

Median, Maximum, and Minimum Ponatinib Exposure at Steady-State by Dose Group: PK Evaluable Population Dose	Median Cmax (Range) (nM)	Median Cmin (Range) (nM)
15 mg QD (n = 8)	49 (23 – 105)	28 (11 – 68)
30 mg QD (n = 9)	125 (67 – 178)	54 (41 – 89)
45 mg QD (n = 21)	161 (64 – 336)	67 (22 – 137)

clones may be achieved at once daily dosing of 15 mg or 30 mg. The dose intensity-safety relationship indicated that there are significant increases in grade 3 adverse events (hypertension, thrombocytopenia, pancreatitis, neutropenia, rash, ALT increase, AST increase, lipase increase, myelosuppression) over the dose range of 15 to 45 mg once-daily. In vitro, there was no significant inhibition of platelet aggregation with Ponatinib at concentrations seen clinically and up to 0.7 μg/mL (1.23 μM).

Cardiac Electrophysiology

A QT assessment was performed in 39 patients with cancer who received 30 mg, 45 mg, or 60 mg Ponatinib once daily. No large changes in the mean QTc interval (i.e., > 20 msec) from baseline were detected in the study. However, a small increase in the mean QTc interval (i.e., < 10 msec) cannot be excluded because of study design limitations. In a phase 3 trial comparing Ponatinib with imatinib, the mean change from baseline to worst QTcF value in Ponatinib-treated patients (n=124) was < 10 msec.

Pharmacokinetics

The geometric mean (CV%) Cmax and AUC(0-) of Ponatinib 45 mg daily at presumed steady state in patients with advanced hematologic malignancies were 73 ng/mL (74%) and 1253 ng•hr/mL (73%), respectively. Ponatinib administered as an investigational capsule formulation to patients with cancer exhibited approximately dose proportional increases in both Cmax and AUC over the dose range of 15 to 60 mg. A dose intensity safety analysis showed a significant increase in grade 3 or higher adverse reactions (i.e., thrombocytopenia, neutropenia, rash, ALT elevation, AST elevation, pancreatitis, and lipase elevation) with an increase in dose intensity.

Absorption

The absolute bioavailability of Ponatinib is unknown. Peak concentrations of Ponatinib are observed within 6 hours after Ponatinib oral administration. Following ingestion of either a high-fat or low-fat meal by 22 healthy volunteers, plasma Ponatinib exposures (AUC and Cmax) were not different when compared to fasting conditions.

Distribution

Ponatinib is greater than 99% bound to plasma proteins in vitro. There was no plasma protein binding displacement of Ponatinib (145 nM) in vitro by other highly protein bound medications (Ibuprofen, Nifedipine, Propranolol, Salicylic Acid, and Warfarin). The geometric mean (CV%) apparent steady state volume of distribution is 1223 liters (102%) following oral administration of Ponatinib 45 mg once daily for 28 days in patients with cancer. Ponatinib is a weak substrate for both P-gp and ABCG2 in vitro. Ponatinib is not a substrate for organic anion transporting polypeptides (OATP1B1, OATP1B3) and organic cation transporter 1 (OCT1) in vitro.

Metabolism

At least 64% of a Ponatinib dose undergoes phase I and phase II metabolism. CYP3A4 and to a lesser extent CYP2C8, CYP2D6 and CYP3A5 are involved in the phase I metabolism of Ponatinib in vitro. Ponatinib is also metabolized by esterases and/or amidases.

Elimination

The geometric mean (range) terminal elimination half-life of Ponatinib was approximately 24 (12 to 66) hours following Ponatinib 45 mg oral administration once daily for 28 days in patients with cancer. Exposure increased by approximately 90% (median) [range: 20% to 440%] between the first dose and presumed steady state. Ponatinib is mainly eliminated via feces. Following a single oral dose of [^{14}C]-labeled Ponatinib, approximately 87% of the radioactive dose is recovered in the feces and approximately 5% in the urine.

THERAPEUTIC INDICATION

Ponatinib is a prescription medication which is a kinase inhibitor indicated for the treatment:

- Adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) that is resistant or intolerant to prior tyrosine kinase inhibitor therapy.
- Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) that is resistant or intolerant to prior tyrosine kinase inhibitor therapy.

DOSAGE AND ADMINISTRATION

Recommended Dosage

The optimal dose of Ponatinib has not been identified. In clinical trials, the starting dose of Ponatinib was 45 mg administered orally once daily. However, in the phase 2 trial, 68% of the patients required dose reductions to 30 mg or 15 mg once daily during the course of therapy. Start dosing with 45 mg once daily. Consider reducing the dose of Ponatinib for patients with chronic phase (CP) CML and accelerated phase (AP) CML who have achieved a major cytogenetic response. Consider discontinuing Ponatinib if response has not occurred by months (90 days). Ponatinib may be taken with or without food. Tablets should be swallowed whole.

Dose Modifications for Myelosuppression

Suggested dose modifications for neutropenia (ANC* less than 1.0 x 109/L) and thrombocytopenia (platelet less than 50 x 109/L) that are unrelated to leukemia are summarized in Table

ANC* < 1 x 109/L or platelet < 50 x 109/L	***First occurrence:*** Interrupt Ponatinib and resume initial 45 mg dose after recovery to ANC 1.5 x 109/L and platelet 75 x 109/L
	Second occurrence: Interrupt Ponatinib and resume at 30 mg after recovery to ANC 1.5 x 109/L and platelet 75 x 109/L
	Third occurrence: Interrupt Ponatinib and resume at 15 mg after recovery to ANC 1.5 x 109/L and platelet 75 x 109/L

*ANC = absolute neutrophil count

Dose Modifications for Non-Hematologic Adverse Reactions

If a serious non-hematologic adverse reaction occurs, modify the dose or interrupt treatment. Do not restart Ponatinib in patients with arterial or venous occlusive reactions unless the potential benefit outweighs the risk of recurrent arterial or venous occlusions and the patient has no other treatment options. For serious reactions other than arterial or venous occlusion, do not restart Ponatinib until the serious event has resolved or the potential benefit of resuming therapy is judged to outweigh the risk.

Hepatotoxicity: Recommended modifications for hepatotoxicity are summarized in Table 2.

Table 2: Recommended Dose Modifications for Hepatotoxicity

Elevation of liver transaminase > 3 x ULN* (Grade 2 or higher)	Occurrence at 45 mg: Interrupt Ponatinib and monitor hepatic function Resume Ponatinib at 30 mg after recovery to Grade 1 (< 3 ULN) Occurrence at 30 mg: Interrupt Ponatinib and resume at 15 mg after recovery to Grade 1 Occurrence at 15 mg: 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

*ULN = Upper Limit of Normal for the lab

Pancreatitis and Elevation of Lipase

Recommended modifications for pancreatic adverse reactions are summarized in Table 3

Table 3: Recommended Dose Modifications for Pancreatitis and Elevation of Lipase

Asymptomatic Grade 1 or 2 elevation of serum lipase	Consider interruption or dose reduction of Ponatinib
Asymptomatic Grade 3 or 4 elevation of lipase (> 2 x ULN*) or asymptomatic radiologic pancreatitis (Grade 2 pancreatitis)	Occurrence at 45 mg: • Interrupt Ponatinib and resume at 30 mg after recovery to Grade 1 (< 1.5 x ULN) Occurrence at 30 mg: • Interrupt Ponatinib and resume at 15 mg after recovery to Grade 1 Occurrence at 15 mg: • Discontinue Ponatinib
Symptomatic Grade 3 pancreatitis	Occurrence at 45 mg: • Interrupt Ponatinib and resume at 30 mg after complete resolution of symptoms and after recovery of lipase elevation to Grade 1 Occurrence at 30 mg: • Interrupt Ponatinib and resume at 15 mg after complete resolution of symptoms and after recovery of lipase elevation to Grade 1 Occurrence at 15 mg: • Discontinue Ponatinib
Grade 4 pancreatitis	Discontinue Ponatinib

*ULN = Upper Limit of Normal for the lab

Dose Modification for Use with Strong CYP3A Inhibitors

The recommended dose should be reduced to 30 mg once daily when administering Ponatinib with strong CYP3A inhibitors

Dose Modification for Use in Patients with Hepatic Impairment

The recommended starting dose is 30 mg once daily in patients with hepatic impairment (Child-Pugh A, B, or C)

WARNINGS AND PRECAUTIONS

Arterial Occlusion

Arterial occlusions, including fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease have occurred in at least 35% of Ponatinib-treated patients from the phase 1 and phase 2 trials. With a minimum of 48 months follow-up for ongoing patients (N=133) in the phase 2 trial, 33% (150/449) of Ponatinib treated patients experienced a cardiac vascular (21%), peripheral vascular (12%), or cerebrovascular (9%) arterial occlusive event; some patients experienced more than 1 type of arterial occlusive event.

Ponatinib can cause fatal and life-threatening arterial occlusion within 2 weeks of starting treatment, and at dose levels as low as 15 mg per day. Ponatinib can also cause recurrent or multi-site vascular occlusion. Patients have required revascularization procedures (coronary, cerebrovascular, and peripheral arterial).

Venous Thromboembolism

Venous thromboembolic events occurred in 6% (25/449) of Ponatinib-treated patients, including deep venous thrombosis (10 patients), pulmonary embolism (7 patients), superficial thrombophlebitis (3 patients), and retinal vein thrombosis (2 patients) with vision loss.

In the phase 2 trial, the incidence of venous thromboembolism was 9% (3/32) in patients with Ph+ ALL, 10% (6/62) in patients with blast phase (BP) CML, 4% (3/85) in patients with AP-CML, and 5% (13/270) in patients with CP-CML. Consider dose modification or discontinuation of Ponatinib in patients who develop serious venous thromboembolism.

Heart Failure

Fatal or serious heart failure or left ventricular dysfunction occurred in 6% of Ponatinib-treated patients (N=29/449) in the phase 2 trial (48 months follow-up). Nine percent of patients (N=39) experienced any grade of heart failure or left ventricular dysfunction. The most frequently reported heart failure events were congestive cardiac failure and decreased ejection fraction (in 14 patients each; 3%).

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.

Hepatotoxicity

Ponatinib can cause hepatotoxicity, including liver failure and death. Fulminant hepatic failure leading to death occurred in an Ponatinib-treated patient within one week of starting Ponatinib. Two additional fatal cases of acute liver failure also occurred. The fatal cases occurred in patients with blast phase (BP) CML or Ph+ ALL. Severe (grade 3 or 4) hepatotoxicity occurred in all disease cohorts.

With 48 months follow-up, 11% (50/449) of Ponatinib-treated patients experienced grade 3 or 4 hepatotoxicity in the phase 2 trial. The most common forms of hepatotoxicity were elevations of aspartate aminotransferase (AST) or alanine aminotransferase (ALT), bilirubin, and alkaline phosphatase. The incidence of AST or ALT elevation was 54% (all grades) and 8% (grade 3 or 4). ALT or AST elevation was not reversed by the date of last follow-up in 5% of patients.

Hepatotoxic events were observed in 29% of patients. The median time to onset of hepatotoxicity event was 3 months, with a range of <1 month to 47 months. Monitor liver function tests at baseline, then at least monthly or as clinically indicated. Interrupt, reduce or discontinue Ponatinib as clinically indicated.

Hypertension

Treatment-emergent elevation of systolic or diastolic blood pressure (BP) occurred in 68% (306/449) of patients in the phase 2 clinical trial (48 months of follow-up). Fifty-three patients (12%) treated with Ponatinib in this clinical trial experienced treatment-emergent symptomatic hypertension as a serious adverse reaction, including hypertensive crisis. Patients may require urgent clinical intervention for hypertension associated with confusion, headache, chest pain, or shortness of breath.

In patients with baseline systolic BP<140 mm Hg and baseline diastolic BP<90 mm Hg, 80% (229/285) experienced treatment-emergent hypertension; 44% (124/285) developed Stage 1 hypertension (defined as systolic BP 140 mm Hg or diastolic BP 90 mm Hg) while 37% developed Stage 2 hypertension (defined as systolic BP 160 mm Hg or diastolic BP 100 mm Hg). In 132 patients with Stage 1 hypertension at baseline, 67% (88/132) developed Stage 2 hypertension.

Monitor and manage blood pressure elevations during Ponatinib use and treat hypertension to normalize blood pressure. Interrupt, dose reduce, or stop Ponatinib if hypertension is not medically controlled. In the event of significant worsening, labile or treatment-resistant hypertension, interrupt treatment and consider evaluating for renal artery stenosis.

Pancreatitis

Pancreatitis occurred in 7% (31/449, 6% serious or grade 3/4) of Ponatinib-treated patients with 48 months of follow-up in the phase 2 trial. The incidence of treatment-emergent lipase elevation was 42% (16% grade 3 or greater). Pancreatitis resulted in discontinuation or treatment interruption in 6% of patients (26/449). The median time to onset of pancreatitis was 14 days (range: 3 - 1452). Twenty-three of the 31 cases of pancreatitis resolved within 2 weeks with dose interruption or reduction.

Check serum lipase every 2 weeks for the first 2 months and then monthly thereafter or as clinically indicated. Consider additional serum lipase monitoring in patients with a history of pancreatitis or alcohol abuse. Dose interruption or reduction may be required. In cases where lipase elevations are accompanied by abdominal symptoms, interrupt treatment with Ponatinib and evaluate patients for pancreatitis Do not consider restarting Ponatinib until patients have complete resolution of symptoms and lipase levels are less than 1.5 x ULN.

Increased Toxicity in Newly Diagnosed Chronic Phase CML

In a prospective randomized clinical trial in the first line treatment of newly diagnosed patients with chronic phase (CP) CML, single agent Ponatinib 45 mg once-daily increased the risk of serious adverse reactions 2-fold compared to single agent imatinib 400 mg once-daily. The median exposure to treatment was less than 6 months. The trial was halted for safety in October 2013.

Arterial and venous thrombosis and occlusions occurred at least twice as frequently in the Ponatinib arm compared to the imatinib arm. Compared to imatinib-treated patients, Ponatinib-treated patients exhibited a greater incidence of myelosuppression, pancreatitis, hepatotoxicity, cardiac failure, hypertension, and skin and subcutaneous tissue disorders. Ponatinib is not indicated and is not recommended for the treatment of patients with newly diagnosed CP-CML.

Neuropathy

Peripheral and cranial neuropathy have occurred in Ponatinib-treated patients. Overall, 20% (90/449) of Ponatinib-treated patients in the pivotal phase 2 trial experienced a peripheral neuropathy event of any grade (2%, grade 3/4) (48 months follow-up). The most common peripheral neuropathies reported were paresthesia (5%, 23/449), neuropathy peripheral (4%,19/449), hypoesthesia (3%, 15/449), dysgeusia (2%, (10/449), muscular weakness (2% (10/449) and hyperesthesia (1%, 5/449). Cranial neuropathy developed in 2% (10/449) of Ponatinib-treated patients (<1%, 3/449 - grade 3/4). Of the patients who developed neuropathy, 26% (23/90) developed neuropathy during the first month of treatment. Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain or weakness. Consider interrupting Ponatinib and evaluate if neuropathy is suspected.

Ocular Toxicity

Serious ocular toxicities leading to blindness or blurred vision have occurred in Ponatinib-treated patients in the phase 2 trial (48 months follow-up). Retinal toxicities including macular edema, retinal vein occlusion, and retinal hemorrhage occurred in 2% of Ponatinib-treated patients. Conjunctival irritation, corneal erosion or abrasion, dry eye, conjunctivitis, conjunctival hemorrhage, hyperaemia and edema or eye pain occurred in 14% of patients. Visual blurring occurred in 6% of patients. Other ocular toxicities include cataracts, periorbital edema, blepharitis, glaucoma, eyelid edema, ocular hyperaemia, iritis, iridocyclitis, and ulcerative keratitis. Conduct comprehensive eye exams at baseline and periodically during treatment.

Hemorrhage

Serious hemorrhage events including fatalities, occurred in 6% (28/449) of patients treated with Ponatinib in the phase 2 trial, with 48 months follow-up. Hemorrhage occurred in 28% (124/449) of patients. The incidence of serious bleeding events was higher in patients with AP-CML, BP-CML, and Ph+ ALL. Gastrointestinal hemorrhage and subdural hematoma were the most commonly reported serious bleeding events occurring in 1% (4/449 and 4/449, respectively). Most hemorrhagic events, but not all, occurred in patients with grade 4 thrombocytopenia.

Fluid Retention

Fluid retention events judged as serious occurred in 4% (18/449) of patients treated with Ponatinib in the phase 2 trial (48 months follow-up). One instance of brain edema was fatal. For fluid retention events occurring in more than 2% of the patients (treatment-emergent), serious cases included: pleural effusion (7/449, 2%), pericardial effusion (4/449, 1%), and edema peripheral (2/449, <1%). In total, fluid retention occurred in 31% of the patients. The most common fluid retention events were peripheral edema (17%), pleural effusion (8%), pericardial effusion (4%) and peripheral swelling (3%). Monitor patients for fluid retention and manage patients as clinically indicated. Interrupt, reduce, or discontinue Ponatinib as clinically indicated.

Cardiac Arrhythmias

Arrhythmias occurred in 19% (86/449) of Ponatinib-treated patients, of which 7% (33/449) were grade 3 or greater. Arrhythmia of ventricular origin was reported in 3% (3/86) of all arrhythmias, with one case being grade 3 or greater. Symptomatic bradyarrhythmia's that led to pacemaker implantation occurred in 1% (3/449) of Ponatinib-treated patients. Atrial fibrillation was the most common arrhythmia and occurred in 7% (31/449) of patients, approximately half of which were grade 3 or 4. Other grade 3 or 4 arrhythmia events included syncope (9 patients; 2.0%), tachycardia and bradycardia (2 patients each 0.4%), and electrocardiogram QT prolonged, atrial flutter , supraventricular tachycardia, ventricular tachycardia, atrial tachycardia, atrioventricular block complete, cardio-respiratory arrest, loss of consciousness, and sinus node dysfunction (1 patient each 0.2%). For 27 patients, the event led to hospitalization. In patients with signs and symptoms suggestive of slow heart rate (fainting, dizziness) or rapid heart rate (chest pain, palpitations or dizziness), interrupt Ponatinib and evaluate.

Myelosuppression

Myelosuppression was reported as an adverse reaction in 59% (266/449) of patients, and severe (grade 3 or 4) myelosuppression occurred in 50% (226/449) of patients treated with Ponatinib. With 48 months of follow-up, the incidence of these events was greater in patients with AP-CML, BP-CML, and Ph+ ALL than in patients with CP-CML.

Severe myelosuppression (Grade 3 or 4) was observed early in treatment, with a median onset time of 1 month (range <1–40 months). Obtain complete blood counts every 2 weeks for the first 3 months and then monthly or as clinically indicated, and adjust the dose as recommended.

Tumor Lysis Syndrome

Two patients (<1%) treated with Ponatinib developed serious tumor lysis syndrome. One case occurred in a patient with advanced AP-CML and one case occurred in a patient with BP-CML. Hyperuricemia occurred in 7% (31/449) of patients. Due to the potential for tumor lysis syndrome in patients with advanced disease (AP-CML, BP-CML, or Ph+ ALL), ensure adequate hydration and treat high uric acid levels prior to initiating therapy with Ponatinib.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

Post marketing cases of reversible posterior leukoencephalopathy syndrome (RPLS – also known as Posterior Reversible Encephalopathy Syndrome - PRES) have been reported in Ponatinib-treated patients. RPLS is a neurological disorder that can present with signs and symptoms such as seizure, headache, decreased alertness, altered mental functioning, vision loss and other visual and neurological disturbances. Hypertension is often present and diagnosis is made with supportive findings on magnetic resonance imaging (MRI) of the brain. If RPLS is diagnosed, interrupt Ponatinib treatment and resume treatment only once the event is resolved and if the benefit of continued treatment outweighs the risk of RPLS.

Compromised Wound Healing and Gastrointestinal Perforation

No formal studies of the effect of Ponatinib on wound healing have been conducted. Based on the mechanism of action Ponatinib could compromise wound healing. Serious gastrointestinal perforation (fistula) occurred in one patient 38 days post-cholecystectomy. Interrupt Ponatinib for at least 1 week prior to major surgery. The decision when to resume Ponatinib after surgery should be based on clinical judgment of adequate wound healing.

Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal studies, Ponatinib can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, oral administration of Ponatinib to pregnant rats during organogenesis caused adverse developmental effects at exposures lower than human exposures at the recommended human dose. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with Ponatinib and for 3 weeks after the last dose.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on its mechanism of action and findings in animals, Ponatinib can cause fetal harm when administered to a pregnant woman. There are no available data on Ponatinib use in pregnant women. In animal reproduction studies, oral administration of Ponatinib to pregnant rats during organogenesis caused adverse developmental effects at doses lower than human exposures at the recommended human dose. Advise pregnant women of the potential risk to a fetus.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown.

Lactation

Risk Summary

There is no data on the presence of Ponatinib in human milk, the effects on the breastfed infant or on milk production. Because of the potential for serious adverse reactions in breastfed infants from Ponatinib including arterial occlusion, venous thromboembolism, heart failure, and hepatotoxicity, advise women not to breastfeed during treatment with Ponatinib and for 6 days following the last dose.

Females and Males of Reproductive Potential

Ponatinib can cause fetal harm when administered to pregnant women.

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating Ponatinib treatment.

Contraception

Females: Advise females of reproductive potential to use effective contraception during treatment with Ponatinib and for 3 weeks after the last dose.

Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

Juvenile Animal Toxicity Data. A juvenile toxicity study in 15-day-old rats was conducted with daily oral gavage administration of Ponatinib at 0.75, 1.5, or 3 mg/kg/day for 21 days. There were no adverse effects of Ponatinib on juvenile rat developmental parameters (vaginal opening, preputial separation or bone measurements) observed in this study. Once daily oral administration of 3 mg/kg/day Ponatinib to juvenile rats beginning on Day 15 postpartum (pp) resulted in mortality related to inflammatory effects after 6 to 7 days following initiation of treatment. The dose of 3 mg/kg/day is approximately 0.32 times the clinical dose on a mg/m^2 basis for a child.

Geriatric Use

One hundred and fifty-five of 449 patients (35%) in the clinical trial of Ponatinib were 65 years of age and over. In patients with CP-CML, patients of age 65 years had a lower major cytogenetic response rate (40%) as compared with patients < 65 years of age (65%). In patients with AP-CML, BP-CML, and Ph+ ALL, patients of age 65 years had a similar hematologic response rate (45%) as compared with patients < 65 years of age (44%). Forty percent of patients 65 years had

arterial occlusion events. Patients of age 65 years are more likely to experience adverse reactions including vascular occlusion, decreased platelet count, peripheral edema, increased lipase, dyspnea, asthenia, muscle spasms, and decreased appetite. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or another drug therapy.

Hepatic Impairment

Administer Ponatinib at a dose of 30 mg once daily in patients with hepatic impairment (Child-Pugh A, B, or C) In a single-dose (30 mg) pharmacokinetic (PK) study; compared to subjects with normal liver function, no major differences in Ponatinib PK were observed in subjects with hepatic impairment (Child-Pugh A, B, or C). However, there was an increased overall incidence of adverse reactions (e.g., gastrointestinal disorders, including a case of severe pancreatitis) in the subjects with hepatic impairment following the single 30 mg dose compared to subjects with normal liver function. The safety of multiple Ponatinib doses, or doses higher than 30 mg have not been studied in patients with hepatic impairment.

DRUG INTERACTIONS

Drugs That Are Strong Inhibitors of CYP3A Enzymes

Based on in vitro studies, Ponatinib is a substrate of CYP3A and to a lesser extent CYP2C8 and CYP2D6. In a drug interaction study in healthy volunteers, co-administration of Ponatinib with ketoconazole increased plasma Ponatinib AUC0-inf and Cmax by 78% and 47%, respectively. When administering Ponatinib with strong CYP3A inhibitors (e.g., boceprevir, clarithromycin, conivaptan, grapefruit juice, Indinavir, Itraconazole, Ketoconazole, Lopinavir/Ritonavir, Nefazodone, Nelfinavir, Posaconazole, Ritonavir, Saquinavir, Telaprevir, Telithromycin, Voriconazole), the recommended starting dose should be reduced. Patients taking concomitant strong CYP3A inhibitors may be at increased risk for adverse reactions.

Drugs That Are Strong Inducers of CYP3A Enzymes

Co-administration of strong CYP3A inducers (e.g., Carbamazepine, Phenytoin, Rifampin, and St. John's Wort) with Ponatinib should be avoided unless the benefit outweighs the risk of decreased Ponatinib exposure. Monitor patients for reduced efficacy. Selection of concomitant medication with no or minimal CYP3A induction potential is recommended. In a drug interaction study in healthy volunteers, co-administration of Ponatinib following multiple doses of rifampin resulted in decreased Ponatinib AUC0-inf and Cmax values by 62% and 42%, respectively.

Drugs That Elevate Gastric pH

Ponatinib may be co-administered with gastric pH-elevating medications. In a drug interaction study in healthy volunteers, co administration of Ponatinib following multiple doses of lansoprazole resulted in a minimal (6%) decrease in Ponatinib exposure

Drugs that are Substrates of the P-gp or ABCG2 Transporter Systems

Ponatinib inhibits the P-glycoprotein (P-gp), ATP-binding cassette G2 (ABCG2) [also known as BCRP], and bile salt export pump (BSEP) transporter systems in vitro.

OVERDOSAGE

Overdoses with Ponatinib were reported in clinical trials. One patient was accidentally administered the entire contents of a bottle of study medication via nasogastric tube. The investigator estimated that the patient received 540 mg of Ponatinib. Two hours after the overdose, the patient had an uncorrected QT interval of 520 ms. Subsequent ECGs showed normal sinus rhythm with uncorrected QT intervals of 480 and 400 ms. The patient died 9 days after the overdose from pneumonia and sepsis. Another patient accidentally self-administered 165 mg on cycle 1 day 2. The patient experienced fatigue and non-cardiac chest pain on day 3. Multiple doses of 90 mg per day for 12 days in a patient resulted in pneumonia, systemic inflammatory response, atrial fibrillation, and a moderate pericardial effusion. In the event of an overdose of Ponatinib, stop Ponatinib, observe the patient and provide appropriate supportive treatment.

PHARMACEUTICAL INFORMATION

Storage condition

Store at below 30^{0}C and dry place, away from light and moisture. Keep out of the reach of children.

Presentation & Packaging

Ponatinix 15 Tablet: Each commercial box contains 60 tablets in a HDPE pot.

Ponatinix 45 Tablet: Each commercial box contains 30 tablets in a HDPE pot.

Only for Export

Manufactured By
Beacon Pharmaceuticals Limited
Bhaluka, Mymensingh, Bangladesh

Marketed By
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Dhaka, Bangladesh

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