Pelex™

Ponatinib Hydrochloride INN

Jenphar Bangladesh | جنفار بنغلاديش

Composition:
Pelex™ 15 Tablet: Each film coated tablet contains Ponatinib Hydrochloride INN equivalent to Ponatinib 15 mg.
Pelex™ 45 Tablet: Each film coated tablet contains Ponatinib Hydrochloride INN equivalent to Ponatinib 45 mg.

Pharmacology:
Ponatinib is a kinase inhibitor. Ponatinib inhibits the in-vitro tyrosine kinase activity of ABL and T315I mutant ABL with IC_{50} concentrations of 0.4 nM and 2.0 nM, respectively. Ponatinib inhibits the in-vitro activity of additional kinases with IC_{50} concentrations between 0.1 nM and 20 nM, including members of the VEGFR, PDGFR, FGFR, EPH receptors and SRC families of kinases and KIT, RET, TIE2 and FLT3. Ponatinib inhibits the in-vitro viability of cells expressing native or mutant BCR-ABL, including T315I.

Indications:
Ponatinib is indicated for the treatment of adult patients with:
- Chronic phase (CP) chronic myeloid leukemia (CML) with resistance or intolerance to at least two prior kinase inhibitors.
- Accelerated phase (AP) or blast phase (BP) CML or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) for whom no other kinase inhibitors are indicated.
- T315I-positive CML (chronic phase, accelerated phase or blast phase) or T315I-positive Ph+ ALL.

Dose & administration:
Dose:
- Recommended Dose in CP-CML: Starting dose is 45 mg orally once daily with a reduction to 15 mg once daily upon achievement of ≤1% BCR-ABL1IS.
- Recommended Dose in AP-CML, BP-CML & Ph+ ALL: Starting dose is 45 mg orally once daily.
- Hepatic Impairment: Reduce the starting dose to 30 mg orally once daily.
- Ponatinib may be taken with or without food.

Dose Modification:

Table 1: Recommended Ponatinib Dosage for Co-administration of Strong CYP3A Inhibitor

Current Ponatinib Dosage	Recommended Ponatinib Dosage with a Strong CYP3A Inhibitor
45 mg orally once daily	30 mg orally once daily
30 mg orally once daily	15 mg orally once daily
15 mg orally once daily	10 mg orally once daily
10 mg orally once daily	Avoid Co-administration of Ponatinib with a strong CYP3A inhibitor

Dose for Patients with Hepatic Impairment:
Reduce the starting dose of Ponatinib from 45 mg orally once daily to 30 mg orally once daily in patients with pre-existing hepatic impairment (Child-Pugh A, B, or C).

Contraindication:
None.

Warnings & precautions:
- *Hypertension:* Monitor blood pressure and manage hypertension as clinically indicated. Interrupt, dose reduce or stop Ponatinib if hypertension is not medically controlled.
- *Pancreatitis:* Monitor serum lipase. Interrupt, then resume at the same or reduced dose discontinue Ponatinib based on severity. Evaluate for pancreatitis when lipase elevation is accompanied by abdominal symptoms.
- *Neuropathy:* Monitor for symptoms of peripheral and cranial neuropathy. Interrupt, then resume at the same or reduced dose or discontinue Ponatinib based on recurrence/severity.
- *Ocular Toxicity:* Conduct comprehensive eye exams at baseline and periodically during treatment.
- *Hemorrhage:* Monitor for hemorrhage and manage patients as clinically indicated. Interrupt, then resume at the same or reduced dose or discontinue Ponatinib based on recurrence/severity.
- *Fluid Retention:* Monitor for fluid retention and manage patients as clinically indicated. Interrupt, then resume at the same or reduced dose or discontinue Ponatinib based on recurrence/severity.
- *Cardiac Arrhythmias:* Monitor for signs or symptoms of arrhythmias and manage patients as clinically indicated. Interrupt, then resume at the same or reduced dose or discontinue Ponatinib based on recurrence/severity.
- *Myelosuppression:* Obtain complete blood counts every 2 weeks for the first 3 months and then monthly or as clinically indicated. If ANC less than 1 x 10^9/L or platelets less than 50 x 10^9/L, interrupt Ponatinib until ANC at least 1.5 x 10^9/L and platelets at least 75 x 10^9/L, then resume at same or reduced dose.
- *Tumor Lysis Syndrome:* Ensure adequate hydration and correct elevated uric acid levels prior to initiating Ponatinib.
- *Reversible Posterior Leukoencephalopathy Syndrome (RPLS):* Interrupt Ponatinib until resolution. The safety of resumption of Ponatinib in patients upon resolution of RPLS is unknown.
- *Impaired Wound Healing and Gastrointestinal Perforation:* Withhold Ponatinib for at least 1 week prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of Ponatinib after resolution of wound healing complications has not been established.
- *Embryo-Fetal Toxicity:* Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception.

Adverse reactions:
The most common (>20%) adverse reactions are rash and related conditions, arthralgia, abdominal pain, headache, constipation, dry skin, hypertension, fatigue, fluid retention and edema, pyrexia, nausea, pancreatitis/lipase elevation, hemorrhage, anemia, hepatic dysfunction and AOEs. The most common Grade 3 or 4 laboratory abnormalities (>20%) are platelet count decreased, neutrophil cell count decreased and white blood cell decreased.

Use in Special Population:
Pregnancy: Based on findings in animals and its mechanism of action. Ponatinib can cause fetal harm when administered to a pregnant woman. There are no available data on Ponatinib use in pregnant women.
Nursing Mothers: There is no data on the presence of Ponatinib in human milk or the effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in the breastfed child from Ponatinib, advise women not to breastfeed during treatment with Ponatinib and for 6 days following the last dose.

Pediatric Use: Safety and effectiveness have not been established in pediatric patients.

Hepatic Impairment: Patients with hepatic impairment are more likely to experience adverse reactions compared to patients with normal hepatic function. Reduce the starting dose of Ponatinib for patients with preexisting hepatic impairment (Child-Pugh A, B, or C). The safety of multiple doses, or doses higher than 30 mg, has not been studied in patients with hepatic impairment.

Renal Impairment: Ponatinib has not been studied in patients with severe renal impairment. Although renal excretion is not a major route of Ponatinib elimination, the potential for severe renal impairment to affect hepatic elimination has not been determined.

Drug interactions:
Effects of Other Drugs on Ponatinib
Strong CYP3A Inhibitors: Co-administration of Ponatinib with a strong CYP3A inhibitor increases Ponatinib plasma concentrations, which may increase the risk of Ponatinib adverse reactions. Avoid Co-administration of Ponatinib with strong CYP3A inhibitors. If Co-administration of Ponatinib with strong CYP3A inhibitors cannot be avoided, reduce the Ponatinib dosage.

Strong CYP3A Inducers: Co-administration of Ponatinib with a strong CYP3A inducer decreases Ponatinib plasma concentrations. Avoid Co-administration of Ponatinib with strong CYP3A inducers 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.

Overdose:
Overdoses with Ponatinib were reported in clinical trials. One patient was estimated to have been administered 540 mg via nasogastric tube. Two hours after the over dosage, the patient had an uncorrected QT interval of 520 ms. Subsequent ECGs showed normal sinus rhythm with uncorrected QT intervals of 480 ms and 400 ms. The patient died 9 days after the over dosage from pneumonia and sepsis. Another patient 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 overdosage, stop Ponatinib, observe the patient and provide supportive treatment as appropriate.

Storage:
Store in a cool & dry place below 30° C, protect from light. Keep out of the reach of children.

Packing:
Pelex™ 15 Tablet: Each box contains 30 tablets and one packet silica gel in a sealed HDPE container.
Pelex™ 45 Tablet: Each box contains 30 tablets and one packet silica gel in a sealed HDPE container.

Manufactured by:
Jenphar Bangladesh Ltd.
Sreepur, Gazipur, Bangladesh.

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