Ponaxen

Ponatinib 15 mg & 45 mg

Everest

COMPOSITION

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

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

INDICATIONS AND USAGE

Chronic Myeloid Leukemia (CML)

Ponatinib is indicated in 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 or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.

Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL)

Ponatinib is indicated in 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.

DOSAGE AND ADMINISTRATION

Therapy should be initiated by a physician experienced in the diagnosis and treatment of patients with leukemia. Haematologic support such as platelet transfusion and haematopoietic growth factors can be used during treatment if clinically indicated.

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.

RECOMMENDED DOSAGE

The recommended starting dose is 45 mg of ponatinib once daily. Treatment should be continued as long as the patient does not show evidence of disease progression or unacceptable toxicity. Discontinuing ponatinib should be considered if a complete haematologic response has not occurred by 3 months (90 days).

The risk of arterial occlusive events is likely to be dose-related. Reducing the dose of ponatinib to 15 mg should be considered for CP-CML patients who have achieved a major cytogenetic response taking the following factors into account in the individual patient assessment: cardiovascular risk, side effects of ponatinib therapy, time to cytogenetic response, and BCR-ABL transcript levels. If dose reduction is undertaken, close monitoring of response is recommended.

DOSAGE MODIFICATIONS

Dose modifications or interruption of dosing should be considered for the management of haematological and non-haematological 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.

Dose modifications for neutropenia (ANC* < 1.0 x 10^9/L) and thrombocytopenia (platelet < 50 x 10^9/L) that are unrelated to leukaemia are summarized in Table 1.

Table 1 Dose modifications for myelosuppression

ANC* < 1.0 x 10^9/L or platelet < 50 x 10^9/L	First occurrence: • Ponatinib should be withheld and resumed at the same dose after recovery to ANC ≥ 1.5 x 10^9/L and platelet ≥ 75 x 10^9/L
	Recurrence at 45 mg: • Ponatinib should be withheld and resumed at 30 mg after recovery to ANC ≥ 1.5 x 10^9/L and platelet ≥ 75 x 10^9/L
	Recurrence at 30 mg: • Ponatinib should be withheld and resumed at 15 mg after recovery to ANC ≥ 1.5 x 10^9/L and platelet ≥ 75 x 10^9/L

Table 2 Dose modifications for pancreatitis and elevation of lipase/amylase.

Grade 2 pancreatitis and/or asymptomatic elevation of lipase/amylase	Ponatinib should be continued at the same dose
Grade 3 or 4 asymptomatic elevation of lipase/amylase (> 2.0 x IULN*) only	Occurrence at 45 mg: • Ponatinib should be withheld and resumed at 30 mg after recovery to ≤ Grade 1 (< 1.5 x IULN) Occurrence at 30 mg: • Ponatinib should be withheld and resumed at 15 mg after recovery to ≤ Grade 1 (< 1.5 x IULN) Occurrence at 15 mg: • Ponatinib discontinuation should be considered
Grade 3 pancreatitis	Occurrence at 45 mg: • Ponatinib should be withheld and resumed at 30 mg after recovery to < Grade 2 Occurrence at 30 mg: • Ponatinib should be withheld and resumed at 15 mg after recovery to < Grade 2 Occurrence at 15 mg: • Ponatinib discontinuation should be considered
Grade 4 pancreatitis	Ponatinib should be discontinued
*IULN = institution upper limit of normal	

Table 3 Recommended dose modifications for hepatic toxicity.

Elevation of liver transaminase > 3 × ULN* Persistent grade 2 (longer than 7 days) Grade 3 or higher	Occurrence at 45 mg: • Ponatinib should be interrupted and hepatic function should be monitored • Ponatinib should be resumed at 30 mg after recovery to ≤ Grade 1 (< 3 × ULN), or recovery to pre-treatment grade Occurrence at 30 mg: • Ponatinib should be interrupted and resumed at 15 mg after recovery to ≤ Grade 1, or recovery to pre-treatment grade Occurrence at 15 mg: • Ponatinib should be discontinued
Elevation of AST or ALT ≥ 3 × ULN concurrent with an elevation of bilirubin > 2 × ULN and alkaline phosphatase < 2 × ULN	Ponatinib should be discontinued
*ULN = Upper Limit of Normal for the lab	

Elderly patients

Of the 449 patients in the clinical study of ponatinib, 155 (35%) were ≥ 65 years of age. Compared to patients < 65 years, older patients are more likely to experience adverse reactions.

Hepatic impairment

Patients with hepatic impairment may receive the recommended starting dose. Caution is recommended when administering Ponatinib to patients with hepatic impairment.

Renal 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 < 50 mL/min, or end-stage renal disease.

Paediatric population

The safety and efficacy of ponatinib in patients less than 18 years of age have not been established. No data are available.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

WARNINGS AND PRECAUTIONS

Myelosuppression

Ponatinib is associated with severe (National Cancer Institute Common Terminology Criteria for Adverse Events grade 3 or 4) thrombocytopenia, neutropenia, and anaemia. Most of the patients with grade 3 or 4 platelet count decreased, anaemia or neutropenia, developed it within the first 3 months of treatment. 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.

Ponaxen

Ponatinib 15 mg & 45 mg

Everest

Arterial occlusion

Arterial occlusions, including fatal myocardial infarction, stroke, retinal arterial occlusions associated in some cases with permanent visual impairment or vision loss, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, renal artery stenosis (associated with worsening, labile or treatment-resistant hypertension), 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. Arterial occlusion adverse events were more frequent with increasing age and in patients with history of ischaemia, hypertension, diabetes, or hyperlipidaemia.

In the phase 2 trial (with a minimum of 64 months follow-up), arterial occlusive adverse reactions have occurred in 25% of patients (treatment-emergent frequencies). Some patients experienced more than 1 type of event. Arterial cardiovascular, cerebrovascular, and peripheral vascular occlusive adverse reactions (treatment-emergent frequencies) occurred in 13%, 9%, and 11% of ponatinib-treated patients, respectively.

In the phase 2 trial, serious arterial occlusive adverse reactions occurred in 20% of patients (treatment-emergent frequencies). Serious arterial cardiovascular, cerebrovascular, and peripheral vascular occlusive adverse reactions (treatment-emergent frequencies) occurred in 10%, 7%, and 9% of ponatinib treated patients, respectively.

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 arterial 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 arterial occlusion. A benefit -risk consideration should guide a decision to restart ponatinib therapy.

Venous thromboembolism

Monitoring for evidence of thromboembolism should be performed. Ponatinib should be interrupted immediately in case of thromboembolism. A benefit -risk consideration should guide a decision to restart ponatinib therapy.

Hypertension

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.

Congestive heart failure

Fatal and serious heart failure or left ventricular dysfunction occurred in ponatinib-treated patients, including events related to prior vascular occlusive events. Patients should be monitored for signs or symptoms consistent with heart failure and they should be treated as clinically indicated, including interruption of ponatinib. Discontinuation of ponatinib should be considered in patients who develop serious heart failure.

Hepatotoxicity

Ponatinib may result in elevation in ALT, AST, bilirubin, and alkaline phosphatase. Most patients who had an event of hepatotoxicity had their first event during the first year of treatment. 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

Severe haemorrhage, including fatalities, occurred in ponatinib -treated patients. The incidence of severe bleeding events was higher in patients with AP-CML, BP-CML and Ph+ ALL. Ponatinib should be interrupted and patients evaluated for serious or severe haemorrhage.

Hepatitis B reactivation

Reactivation of hepatitis B in patients who are chronic carriers of this virus has occurred after these patients received BCR-ABL tyrosine kinase inhibitors.

Patients should be tested for HBV infection before initiating treatment with ponatinib. Carriers of HBV who require treatment with ponatinib should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy.

SPECIAL POPULATIONS

Hepatic impairment

Patients with hepatic impairment may receive the recommended starting dose. Caution is recommended when administering ponatinib to patients with hepatic impairment.

Renal impairment

Caution is recommended in when administering ponatinib to patients with estimated creatinine clearance of < 50 mL/min or end-stage renal disease.

Lactose

This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Interaction with other medicinal products and other forms of interaction

Substances that may increase ponatinib serum concentrations.

CYP3A inhibitors

Ponatinib is metabolized by CYP3A4.

Caution should be exercised and a reduction of the starting dose of ponatinib to 30 mg should be considered with concurrent use of strong CYP3A inhibitors such as clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole, and grapefruit juice.

Substances that may decrease ponatinib serum concentrations CYP3A inducers.

Co-administration of strong CYP3A4 inducers such as carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, and St. John's Wort with ponatinib should be avoided, and alternatives to the CYP3A4 inducer should be sought, unless the benefit outweighs the possible risk of ponatinib underexposure.

FERTILITY, PREGNANCY AND LACTATION

Pregnancy

There are no adequate data from the use of ponatinib in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Ponatinib should be used during pregnancy only when clearly necessary. If it is used during pregnancy, the patient must be informed of the potential risk to the foetus.

Breast-feeding

It is unknown whether ponatinib is excreted in human milk. Available pharmacodynamic and toxicological data cannot exclude potential excretion in human milk. Breast-feeding should be stopped during treatment with ponatinib.

Fertility

No human data on the effect of ponatinib on fertility are available. In rats, treatment with ponatinib has shown effects on female fertility and male fertility was not affected. The clinical relevance of these findings to human fertility is unknown.

Adverse Events

The most common serious adverse reactions >2% (treatment-emergent frequencies) were pneumonia, pancreatitis, abdominal pain, atrial fibrillation, pyrexia, myocardial infarction, peripheral arterial occlusive disease, anaemia, angina pectoris, platelet count decreased, febrile neutropenia, hypertension, coronary artery disease, cardiac failure congestive, cerebrovascular accident, sepsis, cellulitis, acute kidney injury, urinary tract infection and lipase increased.

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 ms 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 Conditions

Store in a cool and dry place. Do not store above 30°C. Do not take **PONAXEN** if it is suspected of having been exposed to temperatures greater than 40° C or 104° F.

Keep **PONAXEN** out of the reach and sight of children.

HOW SUPPLIED

PONAXEN 15 Tablet: Each Child-resistant HDPE container contains 30 tablets (each film coated tablet contains Ponatinib Hydrochloride INN equivalent to Ponatinib 15 mg).

PONAXEN 45 Tablet: Each Child-resistant HDPE container contains 30 tablets (each film coated tablet contains Ponatinib Hydrochloride INN equivalent to Ponatinib 45 mg).

Dispensed only in original container and do not use if seal over bottle opening is broken or missing.

Manufactured By

Everest Pharmaceuticals Ltd.

BSCIC, Kanchpur, Narayanganj, Bangladesh

www.everestpharmabd.com