Nilonib-200

Nilotinib INN 200 mg
Capsule

DRUG INTERNATIONAL LTD.

Composition: Each capsule contains Nilotinib 200 mg as Nilotinib Monohydrochloride Monohydrade INN.

Mechanism of Action: Nilotinib is an inhibitor of the BCR-ABL kinase. Nilotinib binds to and stabilizes the inactive conformation of the kinase domain of ABL protein. In vitro, nilotinib inhibited BCR-ABL mediated proliferation of murine leukemic cell lines and human cell lines derived from patients with Ph+ CML. Under the conditions of the assays, nilotinib was able to overcome imatinib resistance resulting from BCR-ABL kinase mutations, in 32 out of 33 mutations tested.

Pharmacokinetics: Steady-state nilotinib exposure was dose-dependent with less than dose-proportional increases in systemic exposure at dose levels higher than 400 mg given as once or twice daily dosing. In adult patients with resistant or intolerant Ph+ CML given Nilonib 400 mg twice daily, the steady-state mean (%CV) Cmax and AUC0-12h were 2260 ng/ml (35%) and 18000 ng•h/ml (33%), respectively.

Absorption: Relative bioavailability of nilotinib capsule is approximately 50%, as compared to an oral drink solution (pH of 1.2 to 1.3). Peak concentrations of nilotinib are reached 3 hours after oral administration. **Distribution:** The blood-to-serum ratio of nilotinib is 0.68. Serum protein binding is approximately 98%. **Metabolism:** Nilotinib is primarily metabolized via CYP3A4-mediated oxidation and to a minor extent by CYP2C8. Nilotinib is the main circulating component in the serum. None of the metabolites contribute significantly to the pharmacological activity of nilotinib. **Excretion:** After a single dose of radiolabeled nilotinib, more than 90% of the administered dose was eliminated within 7 days: 93% of the dose in feces. Parent drug accounted for 69% of the dose.

Indications:

Adult And Pediatric Patients with Newly Diagnosed Ph+ CML-CP: Nilonib (nilotinib) is indicated for the treatment of adult and pediatric patients greater than or equal to 1 year of age with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase.

Adult Patients with Resistant or Intolerant Ph+ CML-CP and CML-AP: Nilonib is indicated for the treatment of adult patients with chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukemia (Ph+ CML) resistant or intolerant to prior therapy that included imatinib.

Pediatric Patients with Resistant or Intolerant Ph+ CML-CP: Nilonib is indicated for the treatment of pediatric patients greater than or equal to 1 year of age with chronic phase Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) with resistance or intolerance to prior tyrosine-kinase inhibitor (TKI) therapy.

Dosage and Administrations:

Dosage in Adult Patients with Newly Diagnosed Ph+ CML-CP: The recommended dose of Nilonib is 300 mg orally twice daily. Or, as directed by the registered physician.

Dosage in Adult Patients with Resistant or Intolerant Ph+ CML-CP and CML-AP: The recommended dose of Nilonib is 400 mg orally twice daily.

Dosage in Pediatric Patients with Newly Diagnosed Ph+ CML-CP Or Resistant or Intolerant Ph+ CML-CP: The recommended dose of Nilonib for pediatric patients is 230 mg/m² orally twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg) (see Table 1). If needed, attain the desired dose by combining different strengths of Nilonib capsules. Continue treatment as long as clinical benefit is observed or until unacceptable toxicity occurs.

Pediatric dosing of Nilonib (230 mg/m² twice daily, maximum single dose of 400 mg)

Body Surface Area (BSA)	Single Dose	Total Daily Dose
Up to 0.32 m²	50 mg	100 mg
0.33 - 0.54 m²	100 mg	200 mg
0.55 - 0.76 m²	150 mg	300 mg
0.77 - 0.97 m²	200 mg	400 mg
0.98 - 1.19 m²	250 mg	500 mg
1.20 - 1.41 m²	300 mg	600 mg
1.42 - 1.63 m²	350 mg	700 mg
≥1.64 m²	400 mg	800

Side Effects: The most common side effects are- Myelosuppression, QT Prolongation, Sudden Deaths, Cardiac and Arterial Vascular Occlusive Events, Pancreatitis and Elevated Serum Lipase, Hepatotoxicity, Electrolyte Abnormalities, Hemorrhage, Fluid Retention.

Contraindications: Nilonib is contraindicated in patients with hypokalemia, hypomagnesemia, or long QT syndrome.

Use in pregnancy and lactation: Nilonib can cause fetal harm when administered to a pregnant woman. So, Females should be advised to inform their healthcare provider if they are pregnant or become pregnant.

Use in child: Safety and effectiveness of Nilonib in pediatric patients have not been established.

Drug Interactions:

Strong CYP3A Inhibitors: Concomitant use with a strong CYP3A inhibitor increased nilotinib concentrations compared to Nilonib alone, which may increase the risk of Nilonib toxicities. Avoid concomitant use of strong CYP3A inhibitors with Nilonib. If patients must be coadministered a strong CYP3A4 inhibitor, reduce Nilonib dose.

Strong CYP3A Inducers: Concomitant use with a strong CYP3A inducer decreased nilotinib concentrations compared to Nilonib alone, which may reduce Nilonib efficacy. Avoid concomitant use of strong CYP3A inducers with Nilonib.

Proton Pump Inhibitors (PPIs): Concomitant use with a PPI decreased nilotinib concentrations compared to Nilonib alone, which may reduce Nilonib efficacy. Avoid concomitant use of PPI with Nilonib. As an alternative to PPIs, use H2 blockers approximately 10 hours before or approximately 2 hours after the dose of Nilonib, or use antacids approximately 2 hours before or approximately 2 hours after the dose of Nilonib.

Drugs That Prolong the QT Interval: Avoid coadministration of Nilonib with agents that may prolong the QT interval such as anti-arrhythmic drugs.

Precautions:

Myelosuppression: Treatment with Nilonib can cause Grade 3/4 thrombocytopenia, neutropenia and anemia. Perform complete blood counts every 2 weeks for the first 2 months and then monthly thereafter or as clinically indicated. Myelosuppression was generally reversible and usually managed by withholding Nilonib temporarily or dose reduction.

QT Prolongation: Nilonib has been shown to prolong cardiac ventricular repolarization as measured by the QT interval on the surface ECG in a concentration-dependent manner. Prolongation of the QT interval can result in a type of ventricular tachycardia called torsade de pointes, which may result in syncope, seizure, and/or death.

Sudden Deaths: Sudden deaths have been reported in 0.3% of patients with CML treated with Nilonib in clinical studies of 5,661 patients. The relative early occurrence of some of these deaths relative to the initiation of Nilonib suggests the possibility that ventricular repolarization abnormalities may have contributed to their occurrence.

Cardiac and Arterial Vascular Occlusive Events: Cardiovascular events, including arterial vascular occlusive events, were reported in a randomized, clinical trial in newly diagnosed CML patients and observed in the postmarketing reports of patients receiving Nilonib therapy. If acute signs or symptoms of cardiovascular events occur, advise patients to seek immediate medical attention. The cardiovascular status of patients should be evaluated and cardiovascular risk factors should be monitored and actively managed during Nilonib therapy according to standard guidelines.

Pancreatitis and Elevated Serum Lipase: Nilonib can cause increases in serum lipase. Patients with a previous history of pancreatitis may be at greater risk of elevated serum lipase. If lipase elevations are accompanied by abdominal symptoms, interrupt dosing and consider appropriate diagnostics to exclude pancreatitis. Test serum lipase levels monthly or as clinically indicated.

Hepatotoxicity: Nilonib may result in hepatotoxicity as measured by elevations in bilirubin, AST, ALT, and alkaline phosphatase. Grade 3-4 elevations of bilirubin, AST, and ALT were reported at a higher frequency in pediatric than in adult patients. Monitor hepatic function tests monthly or as clinically indicated.

Electrolyte Abnormalities: The use of Nilonib can cause hypophosphatemia, hypokalemia, hyperkalemia, hypocalcemia, and hyponatremia. Correct electrolyte abnormalities prior to initiating Nilonib and during therapy. Monitor these electrolytes periodically during therapy.

Tumor Lysis Syndrome: Tumor lysis syndrome cases have been reported in Nilonib treated patients with resistant or intolerant CML. Malignant disease progression, high WBC counts and/or dehydration were present in the majority of these cases. Due to potential for tumor lysis syndrome, maintain adequate hydration and correct uric acid levels prior to initiating therapy with Nilonib.

Effects on Growth and Development in Pediatric Patients: Adverse reactions associated with growth and development can occur in pediatric patients receiving BCR-ABL tyrosine kinase inhibitors. The long-term effect of prolonged treatment with BCR-ABL tyrosine kinase inhibitors on growth and development in pediatric patients are unknown. Therefore, monitor growth and development in pediatric patients receiving BCR-ABL tyrosine kinase inhibitor treatment.

Embryo-Fetal Toxicity: Based on findings from animal studies and its mechanism of action, Nilonib can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of nilotinib to pregnant rats and rabbits during organogenesis caused adverse developmental outcomes including embryo-fetal lethality/fetal effects (small renal papilla, fetal edema, and skeletal variations) in rats and increased resorptions of fetuses and fetal skeletal variations in rabbits at maternal AUCs approximately 2 and 0.5 times, respectively, the AUC in patients receiving the recommended dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for at least 14 days after the last dose.

Overdose: Overdose with nilotinib has been reported, where an unspecified number of Nilonib capsules were ingested in combination with alcohol and other drugs. Events included neutropenia, vomiting, and drowsiness. In the event of overdose, the patient should be observed and appropriate supportive treatment given.

Storage: Store below 30° C in a dry place. Keep out of reach of children.

Packaging: Each box contains 30 capsules in a container.