Nilonix

Nilotinib Hydrochloride Monohydrate INN

COMPOSITION

Nilonix 150 Capsule: Each capsule contains Nilotinib Hydrochloride Monohydrate INN equivalent to Nilotinib 150 mg.

Nilonix 200 Capsule: Each capsule contains Nilotinib Hydrochloride Monohydrate INN equivalent to Nilotinib 200 mg.

Therapeutic Class - Anti Cancer

CLINICAL PHARMACOLOGY

Nilotinib is an inhibitor of the BCR-ABL kinase. Nilotinib binds to and stabilizes the inactive conformation of the kinase domain of ABL protein.

Pharmacokinetics

Absorption and Distribution

The absolute bioavailability of Nilotinib has not been determined. As compared to an oral drink solution (pH of 1.2 to 1.3), relative bioavailability of Nilotinib capsule is approximately 50%. Peak concentrations of Nilotinib are reached 3 hours after oral administration.

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 daily dosing. Daily serum exposure to Nilotinib following 400 mg twice daily dosing at steady state was 35% higher than with 800 mg once daily dosing. Steady state exposure (AUC) of Nilotinib with 400 mg twice daily dosing was 13% higher than with 300 mg twice daily dosing. The average steady state Nilotinib trough and peak concentrations did not change over 12 months. There was no relevant increase in exposure to Nilotinib when the dose was increased from 400 mg twice daily to 600 mg twice daily. The bioavailability of Nilotinib was increased when given with a meal. Compared to the fasted state, the systemic exposure (AUC) increased by 82% when the dose was given 30 minutes after a high fat meal.

Single dose administration of two 200 mg Nilotinib capsules each dispersed in 1 teaspoon of applesauce and administered within 15 minutes was shown to be bioequivalent to a single dose administration of two 200 mg intact capsules. The blood-to-serum ratio of Nilotinib is 0.68. Serum protein binding is approximately 98% on the basis of in vitro experiments.

Median steady-state trough concentration of Nilotinib was decreased by 53% in patients with total gastrectomy compared to patients who had not undergone surgeries.

Pharmacokinetics, Metabolism and Excretion

The apparent elimination half-life estimated from the multiple dose pharmacokinetic studies with daily dosing was approximately 17 hours. Inter-patient variability in Nilotinib AUC was 32% to 64%. Steady state conditions were achieved by Day 8. An increase in serum exposure to Nilotinib between the first dose and steady state was approximately 2-fold for daily dosing and 3.8-fold for twice daily dosing.

Main metabolic pathways identified in healthy subjects are oxidation and hydroxylation. Nilotinib is the main circulating component in the serum. None of the metabolites contribute significantly to the pharmacological activity of Nilotinib.

After a single dose of radiolabeled Nilotinib in healthy subjects, more than 90% of the administered dose was eliminated within 7 days: mainly in feces (93% of the dose). Parent drug accounted for 69% of the dose.

Age, body weight, gender, or ethnic origin did not significantly affect the pharmacokinetics of Nilotinib.

Renal Impairment

Clinical studies have not been performed in patients with impaired renal function. Clinical studies have

excluded patients with serum creatinine concentration greater than 1.5 times the upper limit of the normal range. Since Nilotinib and its metabolites are not renally excreted, a decrease in total body clearance is not anticipated in patients with renal impairment.

Drug-Drug Interactions

In a Phase 1 trial of Nilotinib 400 mg twice daily in combination with imatinib 400 mg daily or 400 mg twice daily, the AUC increased 30% to 50% for Nilotinib and approximately 20% for imatinib.

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. *In vivo,* Nilotinib reduced the tumor size in a murine BCR-ABL xenograft model. Nilotinib inhibited the autophosphorylation of the following kinases at IC50 values as indicated: BCR-ABL (20 to 60 nM), PDGFR (69 nM), c-KIT (210 nM), CSF-1R (125 to 250 nM), and DDR1 (3.7 nM).

INDICATION

Newly Diagnosed Ph+ CML-CP

Nilotinib is indicated for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+CML) in chronic phase. The effectiveness of Nilotinib is based on major molecular response and cytogenetic response rates.

Resistant or Intolerant Ph+ CML-CP and CML-AP

Nilotinib is indicated for the treatment of chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukemia (Ph+CML) in adult patients resistant or intolerant to prior therapy that included Imatinib. The effectiveness of Nilotinib is based on hematologic and cytogenetic response rates.

DOSAGE AND ADMINISTRATION

Recommended Dosing

Nilotinib should be taken twice daily at approximately 12-hour intervals and must be taken on an empty stomach. No food should be consumed for at least 2 hours before the dose is taken and for at least 1 hour after the dose is taken. Advise patients to swallow the capsules whole with water.

For patients who are unable to swallow capsules, the contents of each capsule may be dispersed in 1 teaspoon of applesauce (puréed apple). The mixture should be taken immediately (within 15 minutes) and should not be stored for future use.

Nilotinib may be given in combination with hematopoietic growth factors such as erythropoietin or G-CSF if clinically indicated. Nilotinib may be given with hydroxyurea or anagrelide if clinically indicated.

Dosage in Newly Diagnosed Ph+ CML-CP

The recommended dose of Nilotinib is 300 mg orally twice daily.

Dosage in Resistant or Intolerant Ph+ CML-CP and CML-AP

The recommended dose of Nilotinib is 400 mg orally twice daily.

CONTRAINDICATIONS

Nilotinib is contraindicated in patients with hypokalemia, hypomagnesemia or long QT syndrome.

WARNINGS AND PRECAUTIONS

Myelosuppression

Treatment with Nilotinib 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 Nilotinib temporarily or dose reduction

QT Prolongation

Nilotinib 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. ECGs should be performed at baseline, 7 days after initiation of Nilotinib, and periodically as clinically indicated and following dose adjustments.

Precautions

Nilotinib should not be used in patients who have hypokalemia, hypomagnesemia or long QT syndrome. Before initiating Nilotinib and periodically, test electrolyte, calcium and magnesium blood levels. Hypokalemia or hypomagnesemia must be corrected prior to initiating Nilotinib and these electrolytes should be monitored periodically during therapy.

Significant prolongation of the QT interval may occur when Nilotinib is inappropriately taken with food and/or strong CYP3A4 inhibitors and/or medicinal products with a known potential to prolong QT. Therefore, coadministration with food must be avoided and concomitant use with strong CYP3A4 inhibitors and/or medicinal products with a known potential to prolong QT should be avoided. The presence of hypokalemia and hypomagnesemia may further prolong the QT interval.

Sudden Deaths

Sudden deaths have been reported in 0.3% of patients with CML treated with Nilotinib in clinical studies of 5,661 patients. The relative early occurrence of some of these deaths relative to the initiation of Nilotinib 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 Nilotinib therapy. With a median time on therapy of 60 months in the clinical trial, cardiovascular events, including arterial vascular occlusive events, occurred in 9.3% and 15.2% of patients in the Nilonix 300 and 400 mg twice daily arms, respectively, and in 3.2% in the imatinib arm. These included cases of cardiovascular events including ischemic heart disease-related cardiac events (5.0% and 9.4% in the Nilotinib 300 mg and 400 mg twice daily arms respectively, and 2.5% in the imatinib arm), peripheral arterial occlusive disease (3.6% and 2.9% in the Nilotinib 300 mg and 400 mg twice daily arms respectively, and 0% in the imatinib arm), and ischemic cerebrovascular events (1.4% and 3.2% in the Nilotinib 300 mg and 400 mg twice daily arms respectively, and 0.7% in the imatinib arm). 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 Nilotinib therapy according to standard guidelines.

Pancreatitis and Elevated Serum Lipase

Nilotinib 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

Nilotinib may result in hepatotoxicity as measured by elevations in bilirubin, AST/ALT, and alkaline phosphatase. Monitor hepatic function tests monthly or as clinically indicated

Electrolyte Abnormalities

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

SIDE EFFECTS

The most commonly reported non-hematologic adverse reactions (greater than or equal to 20%) in patients with newly diagnosed Ph+ CML-CP, resistant or intolerant Ph+ CML-CP, or resistant or intolerant Ph+ CML-AP) were nausea, rash, headache, fatigue, pruritus, vomiting, diarrhea, cough, constipation, arthralgia, nasopharyngitis, pyrexia, and night sweats. Hematologic adverse drug reactions include myelosuppression: thrombocytopenia, neutropenia and anemia.

USE IN SPECIFIC POPULATION

Pregnancy

Risk Summary

Based on findings from animal studies and the mechanism of action, Nilotinib can cause fetal harm when administered to a pregnant woman .

There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, administration of Nilotinib to pregnant rats and rabbits during organogenesis caused adverse developmental outcomes including embryo-fetal lethality, fetal effects, and fetal variations in rats and rabbits at maternal exposures (AUC) approximately 2 and 0.5 times, respectively, the exposures in patients at the recommended dose (see Data). Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies are 2-4% and 15-20%, respectively.

Lactation

Risk Summary

No data are available regarding the presence of Nilotinib or its metabolites in human milk or its effects on a breastfed child or on milk production. However, Nilotinib is present in the milk of lactating rats. Because of the potential for serious adverse reactions in a nursing child, advise lactating women not to breastfeed during treatment with Nilonix and for at least 14 days after the last dose.

Females and Males of Reproductive Potential

Pregnancy

Based on animal studies, Nilotinib can cause fetal harm when administered to a pregnant woman. Females of reproductive potential should have a pregnancy test prior to starting treatment with Nilotinib.

Contraception

Females

Based on animal studies, Nilotinib can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with Nilotinib and for at least 14 days after the last dose.

Infertility

The risk of infertility in females or males of reproductive potential has not been studied in humans. In studies in rats and rabbits, the fertility in males and females was not affected.

Pediatric Use

The safety and effectiveness of Nilotinib in pediatric patients have not been established.

Geriatric Use

In the clinical trials of Nilotinib (patients with newly diagnosed Ph+ CML-CP and resistant or intolerant Ph+ CML-CP and CML-AP), approximately 12% and 30% of patients were 65 years or over respectively.

Patients with newly diagnosed Ph+ CML-CP: There was no difference in major molecular response between patients aged less than 65 years and those greater than or equal to 65 years.

Patients with resistant or intolerant CML-CP: There was no difference in major cytogenetic response rate between patients aged less than 65 years and those greater than or equal to 65 years.

Patients with resistant or intolerant CML-AP: The hematologic response rate was 44% in patients less than 65 years of age and 29% in patients greater than or equal to 65 years.

No major differences for safety were observed in patients greater than or equal to 65 years of age as compared to patients less than 65 years.

Cardiac Disorders

In the clinical trials, patients with a history of uncontrolled or significant cardiovascular disease, including recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia, were excluded. Caution should be exercised in patients with relevant cardiac disorders

Hepatic Impairment

Nilotinib exposure is increased in patients with impaired hepatic function. In a study of subjects with mild to severe hepatic impairment following a single dose administration of 200 mg of Nilotinib, the mean AUC values were increased on average of 35%, 35%, and 56% in subjects with mild (Child-Pugh class A, score 5 to 6), moderate (Child-Pugh class B, score 7 to 9) and severe hepatic impairment (Child-Pugh class C, score 10 to 15), respectively, compared to a control group of subjects with normal hepatic function. Table 9 summarizes the Child-Pugh Liver Function Classification applied in this study. A lower starting dose is recommended in patients with hepatic impairment and the QT interval should be monitored closely in these patients.

DRUG INTERACTIONS

Nilotinib is an inhibitor of CYP3A4, CYP2C8, CYP2C9, and CYP2D6. It may also induce CYP2B6, CYP2C8 and CYP2C9. Therefore, Nilotinib may alter serum concentration of other drugs.

OVERDOSAGE

Overdose with Nilotinib has been reported, where an unspecified number of Nilotinib 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.

PHARMACEUTICALS INFORMATION

Storage Conditions

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

Presentation and Packaging

Nilonix 150 Capsule: Each commercial box contains 120 capsules in a HDPE pot.

Nilonix 200 Capsule: Each commercial box contains 120 capsules in a HDPE pot.

LF28801

Only for Export

Manufactured By
Beacon Pharmaceuticals Limited
Bhaluka, Mymensingh, Bangladesh

Marketed By
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