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twice daily arm, and 0.4% of patients in the imatinib arm. GI hemorrhage occurred in 2.9% and 5% of patients in the Nilonib 300 mg twice daily and 400 mg twice daily arms and in 1.4% of patients in the imatinib arm, respectively. Grade 3 or 4 events occurred in 0.7% and 1.4% of patients in the Nilonib 300 mg twice daily and 400 mg twice daily arms, respectively, and in no patients in the imatinib arm. Monitor for signs and symptoms of bleeding and medically manage as needed.

Total Gastrectomy
Since the exposure of Nilonib is reduced in patients with total gastrectomy, perform more frequent monitoring of these patients. Consider dose increase or alternative therapy in patients with total gastrectomy

Lactose
Since the capsules contain lactose, Nilonib is not recommended for patients with rare hereditary problems of galactose intolerance, severe lactase deficiency with a severe degree of intolerance to lactose-containing products, or of glucose-galactose malabsorption.

Monitoring Laboratory Tests
Complete blood counts should be performed every 2 weeks for the first 2 months and then monthly thereafter. Perform chemistry panels, including electrolytes, calcium, magnesium, liver enzymes, lipid profile, and glucose prior to therapy and periodically. Electrocardiograms should be obtained at baseline, 7 days after initiation and periodically thereafter, as well as following dose adjustments. Monitor lipid profiles and glucose periodically during the first year of Nilonib therapy and at least yearly during chronic therapy. Should treatment with any HMG-CoA reductase inhibitor (a lipid lowering agent) be needed to treat lipid elevations, evaluate the potential for a drug-drug interaction before initiating therapy as certain HMG-CoA reductase inhibitors are metabolized by the CYP3A4 pathway. Assess glucose levels before initiating treatment with Nilonib and monitor during treatment as clinically indicated. If test results warrant therapy, physicians should follow their local standards of practice and treatment guidelines.

Fluid Retention
In the randomized trial in patients with newly diagnosed Ph+ CML in chronic phase, severe (Grade 3 or 4) fluid retention occurred in 3.9% and 2.9% of patients receiving Nilonib 300 mg twice daily and 400 mg twice daily, respectively, and in 2.5% of patients receiving imatinib. Effusions (including pleural effusion, pericardial effusion, ascites) or pulmonary edema, were observed in 2.2% and 1.1% of patients receiving Nilonib 300 mg twice daily and 400 mg twice daily, respectively, and in 2.1% of patients receiving imatinib. Effusions were severe (Grade 3 or 4) in 0.7% and 0.4% of patients receiving Nilonib 300 mg twice daily and 400 mg twice daily, respectively, and in no patients receiving imatinib. Similar events were also observed in postmarketing reports. Monitor patients for signs of severe fluid retention (e.g., unexpected rapid weight gain or swelling) and for symptoms of respiratory or cardiac compromise (e.g., shortness of breath) during Nilonib treatment; evaluate etiology and treat patients accordingly.

Effects on Growth and Development in Pediatric
Patients Growth retardation has been reported in pediatric patients with Ph+ CML in chronic phase treated with Nilonib. In a pediatric trial with 58 patients with Ph+ CML in chronic phase with a median exposure of 56.7 months, growth deceleration (crossing at least two main height percentile lines from baseline) was observed in eight patients: five (9%) crossed two main percentile lines from baseline and three (5%) crossed three main percentile lines from baseline (percentile lines: 5th, 10th, 25th, 50th, 75th, 90th, and 95th). Growth deceleration was more pronounced in children who were less than age 12 at baseline. Adverse reactions associated with growth retardation were reported in 3 patients (5%). Monitor growth and development in pediatric patients receiving Nilonib 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 area under the curve (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 14 days after the last dose.

Monitoring of BCR-ABL Transcript Levels
Monitoring of BCR-ABL Transcript Levels in Patients Who Discontinued Nilonib
Monitor BCR-ABL transcript levels in patients eligible for treatment discontinuation using an FDA authorized test validated to measure molecular response levels with a sensitivity of at least MR4.5 (BCR-ABL/ABL ≤ 0.0032% IS). In patients who discontinue Nilonib therapy, assess BCR-ABL transcript levels monthly for one year, then every 6 weeks for the second year, and every 12 weeks thereafter during treatment discontinuation.
Newly diagnosed patients must reinitiate Nilonib therapy within 4 weeks of a loss of major molecular response [(MMR), corresponding to MR3.0 or = BCR-ABL/ABL ≤ 0.1% IS].
Patients resistant or intolerant to prior treatment which included imatinib must reinitiate Nilonib therapy within 4 weeks of a loss of MMR or confirmed loss of MR4.0 (two consecutive measures separated by at least 4 weeks showing loss of MR4.0, corresponding to = BCR-ABL/ABL ≤ 0.01% IS).
For patients who fail to achieve MMR after three months of treatment reinitiation, BCR-ABL kinase domain mutation testing should be performed.

Monitoring of BCR-ABL Transcript Levels in Patients Who Have Reinitiated Therapy After Loss of Molecular Response
Monitor CBC and BCR-ABL transcripts in patients who reinitiate treatment with Nilonib due to loss of molecular response quantitation every 4 weeks until a major molecular response is re-established, then every 12 weeks.

DRUG INTERACTIONS
Effect of Other Drugs on Nilonib
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
Concomitant use with a proton pump inhibitor (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

HOW SUPPLIED
Nilonib 150mg Capsule available in pack size of 60's, 112's & 120's
Nilonib 200mg Capsule available in pack size of 60's, 112's & 120's

DOSAGE:
As directed by the physician.

Instructions:
Store at 25°C, (Excursions permitted between 15°C to 30°C).
Protect from sunlight & moisture.
Keep out of the reach of children.
To be dispensed on the prescription of a registered medical practitioner only.

خوراک :
ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
ہدایات :
دوا کو ۲۵ ڈگری سینٹی گریڈ درجہ حرارت پر رکھیں۔ (درجہ حرارت کی حد ۱۵ سے ۳۰ ڈگری سینٹی گریڈ ہے)۔
دھوپ اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

Kaizen Pharmaceuticals (Pvt.) Ltd.

Manufactured by:
Kaizen Pharmaceuticals (Pvt.) Ltd.
E-127-129, North Western Industrial Zone,
Bin Qasim, Karachi-75020, Pakistan.

Art No. 1514

Nilonib

(Nilotinib Hydrochloride)

150mg & 200mg Capsule

نیلونِب

(نیلوٹینیب ہائیڈروکلورائیڈ)

۱۵۰ ملی گرام اور ۲۰۰ ملی گرام کیپسولز

COMPOSITION:

Nilonib Capsule 150mg
Each capsule contains:
Nilotinib Hydrochloride Monohydrate Eq. to Nilotinib……...150mg

Nilonib Capsule 200mg
Each capsule contains:
Nilotinib Hydrochloride Monohydrate Eq. to Nilotinib……...200mg

WARNING: QT PROLONGATION AND SUDDEN DEATHS

- Nilonib prolongs the QT interval. Prior to Nilonib administration and periodically, monitor for hypokalemia or hypomagnesemia and correct deficiencies. Obtain ECGs to monitor the QTc at baseline, seven days after initiation, and periodically thereafter, and following any dose adjustments.
- Sudden deaths have been reported in patients receiving Nilonib. Do not administer Nilonib to patients with hypokalemia, hypomagnesemia, or long QT syndrome.
- Avoid use of concomitant drugs known to prolong the QT interval and strong CYP3A4 inhibitors.
- Avoid food 2 hours before and 1 hour after taking the dose.

CLINICAL PHARMACOLOGY:
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. 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 (3.7nM).

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. In adult patients with newly diagnosed Ph+ CML given Nilonib 300 mg twice daily, the steady-state mean (% CV) Cmax and AUC0-12h were 1540 ng/mL (48%) and 13337 ng·h/mL (46%), respectively. 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. The average steady state nilotinib trough and peak concentrations did not change over 12 months.

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. Nilotinib is a substrate of P-gp in vitro. Median steady-state trough concentration of nilotinib was decreased by 53% in patients with total gastrectomy compared to patients who had not undergone surgeries.

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Effect of Food
Compared to the fasted state, the systemic exposure (AUC) increased by 82% when the dose was given 30 minutes after a high fat meal (meal of 800 to 1000 calories with fat being 50% of total caloric content; approximately: 150 calories from protein, 250 calories from carbohydrates, and 500-600 calories from fat).
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.

Distribution:
The blood-to-serum ratio of nilotinib is 0.68. Serum protein binding is approximately 98%.

Elimination:
The mean (CV%) apparent elimination half-life is estimated to be approximately 17 hours (69%) and the mean (CV%) apparent clearance approximates 29 L/h (61%). 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.

PHARMACODYNAMICS:
Based on exposure-response analyses for efficacy, a relationship between drug exposure and a greater likelihood of response was observed in clinical studies. Based on exposure-response analyses for safety, a relationship between exposure and a greater likelihood of safety events, including a higher occurrence of total bilirubin elevations, was observed in clinical studies.

Cardiac Electrophysiology
Nilonib is associated with concentration-dependent QT prolongation. At a dose of Nilonib 400 mg twice daily given without food in healthy subjects, the maximum mean placebo-adjusted QTcF changes were 10.4 msec (90% CI: 2.85, 18.0). After a single dose of Nilonib 800 mg (two times the maximum approved recommended dosage) given with a high fat meal to healthy subjects, the maximum mean placebo-adjusted QTcF changes were) 18.0 msec (90% CI: 9.65, 25.8). Peak plasma concentrations in the QT study were 26% lower than or comparable with those observed in patients enrolled in the single-arm study

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

DOSAGE & ADMINISTRATION:
Recommended Dosage
Dose Nilonib twice daily at approximately 12-hour intervals 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.

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

Dosage in Adult Patients with Newly Diagnosed Ph+ CML-CP
The recommended dosage of Nilonib is 300 mg orally twice daily.

Dosage in Adult Patients with Resistant or Intolerant Ph+ CML-CP and CML-AP
The recommended dosage 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 and CML-AP
The recommended dosage 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). 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.

ROUTE OF ADMINISTRATION:
Oral

ADVERSE REACTIONS:
The following clinically significant adverse reactions can occur with Nilonib
- 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

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, observe the patient and provide appropriate supportive treatment.

WARNINGS AND PRECAUTIONS:
Myelosuppression
Treatment with Nilonib can cause Grade 3/4 thrombocytopenia, neutropenia, and anemia. Perform CBCs 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 electrocardiogram (ECG) in a concentration-dependent manner [see Adverse Reactions (6.1), Clinical Pharmacology (12.2)]. 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. Electrocardiograms should be performed at baseline, 7 days after initiation of Nilonib, and periodically as clinically indicated and following dose adjustments.
Nilonib should not be used in patients who have hypokalemia, hypomagnesemia, or long QT syndrome. Before initiating Nilonib and periodically, test electrolyte, calcium, and

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magnesium blood levels. Hypokalemia or hypomagnesemia must be corrected prior to initiating Nilonib and these electrolytes should be monitored periodically during therapy.
Significant prolongation of the QT interval may occur when Nilonib 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 Nilonib in clinical studies of 5661 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. With a median time on therapy of 60 months in the clinical trial, cardiovascular events, including arterial vascular occlusive events, occurred in 9% and 15% of patients in the Nilonib 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% and 9% in the Nilonib 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 Nilonib 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 Nilonib 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 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, aspartate aminotransferase (AST), alanine aminotransferase (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 and following dose adjustments.

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 (TLS) cases have been reported in Nilonib treated patients with resistant or intolerant CML. Malignant disease progression, high white blood cell (WBC) counts and/or dehydration were present in the majority of these cases. Due to potential for TLS, maintain adequate hydration and correct uric acid levels prior to initiating therapy with Nilonib.

Hemorrhage
Serious hemorrhagic events, including fatal events, have occurred in patients with CML treated with Nilonib. In a randomized trial in patients with newly diagnosed Ph+ CML in chronic phase comparing Nilonib and imatinib, Grade 3 or 4 hemorrhage occurred in 1.1% of patients in the Nilonib 300 mg twice daily arm, in 1.8% of patients in the Nilonib 400 mg

BACK