140mm

210mm

NITONIB Capsule

(N i l o t i n i b)

نیٹونب کیپسول

(نیلوٹینیب)

COMPOSITION

Nitonib Capsule 150mg

Each capsule contains:

Nilotinib (as hydrochloride monohydrate).....150mg

(Innovator's Specifications)

Nitonib Capsule 200mg

Each capsule contains:

Nilotinib (as hydrochloride monohydrate).....200mg

(Innovator's Specifications)

DESCRIPTION

Nitonib (nilotinib) capsules, for oral use, contain 150 mg, or 200 mg nilotinib which belongs to a pharmacologic class of drugs known as kinase inhibitors.

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).

INDICATIONS

Newly Diagnosed Ph+ CML-CP

Nitonib (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 Nitonib is based on major molecular response and cytogenetic response rates.

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

Nitonib 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 Nitonib is based on hematologic and cytogenetic response rates.

DOSAGE AND ADMINISTRATION

Recommended Dosing

Nitonib 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.

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

Dosage in Newly Diagnosed Ph+ CML-CP

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

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

The recommended dose of Nitonib (nilotinib) is 400 mg orally twice daily.

Discontinuation of treatment after a sustained molecular response (MR 4.5) on Nitonib

Patient Selection

Eligibility for Discontinuation of Treatment

Ph+ CML-CP patients with typical BCR-ABL transcripts who have been taking Nitonib for a minimum of 3 years and have achieved a sustained molecular response (MR4.5, corresponding to = BCR-ABL/ABL ≤ 0.0032% IS) may be eligible for treatment discontinuation.

Patients with typical BCR-ABL transcripts (i.e., 13a2/b2a2 or e14a2/b3a2) who achieve the sustained MR4.5 criteria are eligible for discontinuation of Nitonib treatment. Patients must continue to be monitored for possible loss of molecular remission after treatment discontinuation. Use the same FDA authorized test to consistently monitor molecular response levels while on and off treatment.

Consider discontinuation of treatment in patients with newly diagnosed Ph+ CML-CP who have:

- been treated with Nitonib for at least 3 years
- maintained a molecular response of at least MR4.0 (corresponding to = BCR-ABL/ABL ≤ 0.01% IS) for one year prior to discontinuation of therapy
- achieved an MR4.5 for the last assessment taken immediately prior to discontinuation of therapy
- been confirmed to express the typical BCR-ABL transcripts (e13a2/b2a2 or e14a2/b3a2)
- no history of accelerated phase or blast crisis
- no history of prior attempts of treatment-free remission discontinuation that resulted in relapse.

Consider discontinuation of treatment in patients with Ph+ CML-CP that are resistant or intolerant to treatment with imatinib who have achieved a sustained molecular response (MR4.5) on Nitonib who have:

- been treated with Nitonib for a minimum of 3 years
- been treated with imatinib only prior to treatment with Nitonib
- achieved a molecular response of MR.4.5 (corresponding to = BCR-ABL/ABL ≤ 0.0032% IS)
- sustained an MR4.5 for a minimum of one year immediately prior to discontinuation of therapy
- been confirmed to express the typical BCR-ABL transcripts (e13a2/b2a2 or e14a2/b3a2)
- no history of accelerated phase or blast crisis
- no history of prior attempts of treatment-free remission discontinuation that resulted in relapse.

Monitor BCR-ABL transcript levels and complete blood count with differential in patients who have discontinued Nitonib therapy monthly for one year, then every 6 weeks for the second year, and every 12 weeks thereafter.

Upon the loss of MR4.0 (corresponding to = BCR-ABL/ABL ≤ 0.01%IS) during the treatment-free phase, monitor BCR-ABL transcript levels every 2 weeks until BCR-ABL levels remain lower than major molecular response (MMR, corresponding to MR3.0 or = BCR-ABL/ABL ≤ 0.1%IS) for 4 consecutive measurements.

The patient can then proceed to the original monitoring schedule.

Re-initiation of treatment in patients who lose molecular response after discontinuation of therapy with Nitonib.

- Newly diagnosed patients who lose MMR must re-initiate treatment within 4 weeks at the dose level prior to discontinuation of therapy. Patients who re-initiate Nitonib therapy should have their BCR-ABL transcript levels monitored monthly until major molecular response is re-established and every 12 weeks thereafter.
- Patients resistant or intolerant to prior treatment that included imatinib with confirmed loss of MR4.0 (2 consecutive measures separated by at least 4 weeks showing loss of MR4.0) or loss of MMR must reinitiate treatment within 4 weeks at the dose level prior to discontinuation of therapy. Patients who re-initiate Nitonib therapy should have their BCR-ABL transcript levels monitored monthly until previous major molecular response or MR 4.0 is re-established and every 12 weeks thereafter.

Dose Adjustments or Modifications

QT Interval Prolongation:

Table 1: Dose Adjustments for QT Prolongation

ECGs with a QTcF greater than 480 msec	1. Withhold Nitonib, and perform an analysis of serum potassium and magnesium, and if below lower limit of normal, correct with supplements to within normal limits. Concomitant medication usage must be reviewed. 2. Resume within 2 weeks at prior dose if QTcF returns to less than 450 msec and to within 20 msec of baseline. 3. If QTcF is between 450 msec and 480 msec after 2 weeks, reduce the dose to 400 mg once daily. 4. Discontinue Nitonib if, following dose-reduction to 400 mg once daily, QTcF returns to greater than 480 msec. 5. An ECG should be repeated approximately 7 days after any dose adjustment.

Myelosuppression

Withhold or dose-reduce Nitonib for hematological toxicities (neutropenia, thrombocytopenia) that are not related to underlying leukemia (Table 2).

Table 2: Dose Adjustments for Neutropenia and Thrombocytopenia

Newly diagnosed Ph+ CML in chronic phase at 300 mg twice daily Resistant or intolerant Ph+ CML in chronic phase or accelerated phase at 400 mg twice daily	ANC* less than 1.0 x 10^9/L and/or platelet counts less than 50 x 10^9 /L	1. Stop Nitonib, and monitor blood counts. 2. Resume within 2 weeks at prior dose if ANC greater than 1.0 x 10^9/L and platelets greater than 50 x 10^9/L. 3. If blood counts remain low for greater than 2. weeks, reduce the dose to 400 mg once daily.

*ANC=absolute neutrophil count

See Table 3 for dose adjustments for elevations of lipase, amylase, bilirubin, and/or hepatic transaminases.

Table 3: Dose Adjustments for Selected Non-Hematologic Laboratory Abnormalities

Elevated serum lipase or amylase greater than or equal to Grade 3	1. Withhold Nitonib, and monitor bilirubin 2. Resume treatment at 400 mg once daily if bilirubin returns to less than or equal to Grade 1
Elevated bilirubin greater than or equal to Grade 3	1. Withhold Nitonib, and monitor serum lipase or amylase 2. Resume treatment at 400 mg once daily if serum lipase or amylase returns to less than or equal to Grade 1
Elevated hepatic transaminases greater than or equal to Grade 3	1. Withhold Nitonib, and monitor hepatic transaminases 2. Resume treatment at 400 mg once daily if hepatic transaminases returns to less than or equal to Grade 1

Other Non-Hematologic Toxicities

If other clinically significant moderate or severe non-hematologic toxicity develops, withhold dosing, and resume at 400 mg once daily when the toxicity has resolved. If clinically appropriate, escalation of the dose back to 300 mg (newly diagnosed Ph+ CML-CP) or 400 mg (resistant or intolerant Ph+ CML-CP and CMLAP) twice daily should be considered. For Grade 3 to 4 lipase elevations, dosing should be withheld, and may be resumed at 400 mg once daily. Test serum lipase levels monthly or as clinically indicated. For Grade 3 to 4 bilirubin or hepatic transaminase elevations, dosing should be withheld, and may be resumed at 400 mg once daily. Test bilirubin and hepatic transaminases levels monthly or as clinically indicated.

Hepatic Impairment

If possible, consider alternative therapies. If Nitonib must be administered to patients with hepatic impairment, consider the following dose reduction:

Table 4: Dose Adjustments for Hepatic Impairment (At Baseline)

Newly diagnosed Ph+ CML in chronic phase at 300 mg twice daily	Mild, Moderate, or Severe*	An initial dosing regimen of 200 mg twice daily followed by dose escalation to 300 mg twice daily based on tolerability
Resistant or intolerant Ph+ CML in chronic phase or accelerated phase at 400 mg twice daily	Mild or Moderate*	An initial dosing regimen of 300 mg twice daily followed by dose escalation to 400 mg twice daily based on tolerability
	Severe*	A starting dose of 200 mg twice daily followed by a sequential dose escalation to 300 mg twice daily and then to 400 mg twice daily based on tolerability

*Mild=mild hepatic impairment (Child-Pugh Class A); Moderate=moderate hepatic impairment (Child-Pugh Class B); Severe=severe hepatic impairment (Child-Pugh Class C)

Concomitant Strong CYP3A4 Inhibitors

Avoid the concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole). Avoid grapefruit products since they may also increase serum concentrations of nilotinib. Should treatment with any of these agents be required, therapy with Nitonib should be interrupted. If patients must be co-administered a strong CYP3A4 inhibitor, based on pharmacokinetic studies, consider a dose reduction to 300 mg once daily in patients with resistant or intolerant Ph+ CML or to 200 mg once daily in patients with newly diagnosed Ph+ CML-CP. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inhibitors. If the strong inhibitor is discontinued, a washout period should be allowed before the Nitonib dose is adjusted upward to the indicated dose. For patients who cannot avoid use of strong CYP3A4 inhibitors, monitor closely for prolongation of the QT interval.

Concomitant Strong CYP3A4 Inducers

Avoid the concomitant use of strong CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, and phenobarbital). Also inform patients not to take St. John's Wort since these agents may reduce the concentration of Nitonib. Based on the nonlinear pharmacokinetic profile of nilotinib, increasing the dose of Nitonib when co-administered with such agents is unlikely to compensate for the loss of exposure.

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.

Pharmacogenomics

Nitonib can increase bilirubin levels. A pharmacogenetic analysis of 97 patients evaluated the polymorphisms of UGT1A1 and its potential association with hyperbilirubinemia during Nitonib treatment. In this study, the (TA)7/(TA)7 genotype was associated with a statistically significant increase in the risk of hyperbilirubinemia relative to the (TA)6/(TA)6 and (TA)6/(TA)7 genotypes. However, the largest increases in bilirubin were observed in the (TA)7/(TA)7 genotype (UGT1A1*28) patients.

QT/QTc Prolongation

In a placebo-controlled study in healthy volunteers designed to assess the effects of Nitonib on the QT interval, administration of Nitonib was associated with concentration-dependent QT prolongation; the maximum mean placebo-adjusted QTcF change from baseline was 18 msec (1-sided 95% Upper CI: 26 msec). A positive control was not included in the QT study of healthy volunteers. Peak plasma concentrations in the QT study were 26% lower than those observed in patients enrolled in the single-arm study.

WARNINGS AND PRECAUTIONS

Myelosuppression

Treatment with Nitonib 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 Nitonib temporarily or dose reduction.

QT Prolongation

Nitonib 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 Nitonib, and periodically as clinically indicated and following dose adjustments.

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

Significant prolongation of the QT interval may occur when Nitonib is inappropriately taken with food and/or strong CYP3A4 inhibitors and/or medicinal products with a known potential to prolong QT. Therefore, co-administration 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 post-marketing 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 Nitonib 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 Nitonib 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 Nitonib 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 Nitonib 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 Nitonib therapy according to standard guidelines.

Pancreatitis and Elevated Serum Lipase

Nitonib 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

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

Drug Interactions

Avoid administration of Nitonib with agents that may increase nilotinib exposure (e.g., strong CYP3A4 inhibitors) or anti-arrhythmic drugs (including, but not limited to amiodarone, disopyramide, procainamide, quinidine and sotalol) and other drugs that may prolong QT interval (including, but not limited to chloroquine, clarithromycin, haloperidol,

methadone, moxifloxacin and pimozide). Should treatment with any of these agents be required, interrupt therapy with Nitonib. If interruption of treatment with Nitonib is not possible, patients who require treatment with a drug that prolongs QT or strongly inhibits CYP3A4 should be closely monitored for prolongation of the QT interval.

Food Effects

The bioavailability of nilotinib is increased with food, thus Nitonib must not be taken with food. No food should be consumed for at least 2 hours before and for at least 1 hour after the dose is taken. Also avoid grapefruit products and other foods that are known to inhibit CYP3A4.

Hepatic Impairment

Nilotinib exposure is increased in patients with impaired hepatic function. Use a lower starting dose for patients with mild to severe hepatic impairment (at baseline) and monitor the QT interval frequently.

Tumor Lysis Syndrome

Tumor lysis syndrome cases have been reported in Nitonib 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 Nitonib.

Hemorrhage

Serious hemorrhagic events, including fatal events, have occurred in patients with CML treated with Nitonib. In a randomized trial in patients with newly diagnosed Ph+ CML in chronic phase comparing Nitonib and imatinib, Grade 3 or 4 hemorrhage occurred in 1.1% of patients in the Nitonib 300 mg twice daily arm, in 1.8% patients in the Nitonib 400 mg twice daily arm, and 0.4% of patients in the imatinib arm. GI hemorrhage occurred in 2.9% and 5.1% of patients in the Nitonib 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 Nitonib 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 nilotinib 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, Nitonib 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. ECGs 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 Nitonib 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 Nitonib and monitor during treatment as clinically indicated. If test results warrant therapy, physician 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 Nitonib 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 Nitonib 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 Nitonib 300 mg twice daily and 400 mg twice daily, respectively, and in no patients receiving imatinib. Similar events were also observed in post-marketing 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 Nitonib treatment; evaluate etiology and treat patients accordingly.

Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, Nitonib 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.

Monitoring of BCR-ABL Transcript Levels

Monitoring of BCR-ABL Transcript Levels in Patients Who Discontinued Nitonib

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 Nitonib 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 Nitonib 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 Nitonib 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 re initiation, 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 re-initiate treatment with Nitonib due to loss of molecular response quantitation every 4 weeks until a major molecular response is re-established, then every 12 weeks.

SIDE EFFECTS

The following serious adverse reactions can occur with Nitonib.

- Myelosuppression
- QT Prolongation
- Sudden Deaths
- Cardiac and Arterial Vascular Occlusive Events
- Pancreatitis and Elevated Serum Lipase
- Hepatotoxicity
- Electrolyte Abnormalities
- Hemorrhage
- Fluid Retention

The following adverse drug reactions were reported in patients in the Nitonib clinical studies at the recommended doses. These adverse drug reactions are ranked under a heading of frequency, the most frequent first using the following convention: common (greater than or equal to1% and less than 10%), uncommon (greater than or equal to 0.1% and less than 1%), and unknown frequency (single events). For laboratory abnormalities, very common events (greater than or equal to 10%) are also reported. These adverse reactions are included based on clinical relevance and ranked in order of decreasing seriousness within each category, obtained from 2 clinical studies:

1. Newly diagnosed Ph+ CML-CP 60 month analysis and,
2. Resistant or intolerant Ph+ CML-CP and CMP-AP 24 months' analysis.

Infections and Infestations: **Common:** folliculitis. Uncommon: pneumonia, bronchitis, urinary tract infection, candidiasis (including oral candidiasis). **Unknown frequency:** hepatitis B reactivation, sepsis, subcutaneous abscess, anal abscess, furuncle, tinea pedis.

Neoplasms Benign, Malignant, and Unspecified: **Common:** skin papilloma. Unknown frequency: oral papilloma, paraproteinemia.

Blood and Lymphatic System Disorders: Common: leukopenia, eosinophilia, febrile neutropenia, pancytopenia, lymphopenia. Unknown frequency: thrombocythemia, leukocytosis.

Immune System Disorders: Unknown frequency: hypersensitivity.

Endocrine Disorders: Uncommon: hyperthyroidism, hypothyroidism. Unknown frequency: hyperparathyroidism secondary, thyroiditis.

Metabolism and Nutrition Disorders: Very Common: hypophosphatemia. Common: electrolyte imbalance (including hypomagnesemia, hyperkalemia, hypokalemia, hyponatremia, hypocalcemia, hypercalcemia, hyperphosphatemia), diabetes mellitus, hyperglycemia, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia. Uncommon: gout, dehydration, increased appetite. Unknown frequency: hyperuricemia, hypoglycemia.

Psychiatric Disorders: Common: depression, anxiety. Unknown frequency: disorientation, confusional state, amnesia, dysphoria.

Nervous System Disorders: Common: peripheral neuropathy, hypoesthesia, and paresthesia. Uncommon: intracranial hemorrhage, ischemic stroke, transient ischemic attack, cerebral infarction, migraine, loss of consciousness (including syncope), tremor, disturbance in attention, hyperesthesia. Unknown frequency: basilar artery stenosis, brain edema, optic neuritis, lethargy, dysesthesia, restless legs syndrome.

Eye Disorders: Common: eye hemorrhage, eye pruritus, conjunctivitis, dry eye (including xerophthalmia).

Uncommon: vision impairment, vision blurred, visual acuity reduced, photopsia, hyperemia (scleral, conjunctival, ocular), eye irritation, conjunctival hemorrhage. **Unknown frequency:** papilledema, diplopia, photophobia, eye swelling, blepharitis, eye pain, chorioretinopathy, conjunctivitis allergic, ocular surface disease.

Ear and Labyrinth Disorders: Common: vertigo. Unknown frequency: hearing impaired, ear pain, tinnitus.

Cardiac Disorders: Common: angina pectoris, arrhythmia (including atrioventricular block, cardiac flutter, extrasystoles, atrial fibrillation, tachycardia, and bradycardia), palpitations, electrocardiogram QT prolonged. Uncommon: cardiac failure, myocardial infarction, coronary artery disease, cardiac murmur, coronary artery stenosis, myocardial ischemia, pericardial effusion, cyanosis. Unknown frequency: ventricular dysfunction, pericarditis, ejection fraction decrease.

Vascular Disorders: Common: flushing. Uncommon: hypertensive crisis, peripheral arterial occlusive disease, intermittent claudication, arterial stenosis limb, hematoma, arteriosclerosis. Unknown frequency: shock hemorrhagic, hypotension, thrombosis, peripheral artery stenosis.

Respiratory, Thoracic and Mediastinal Disorders: Common: dyspnea exertional, epistaxis, dysphonia. Uncommon: pulmonary edema, pleural effusion, interstitial lung disease, pleuritic pain, pleurisy, pharyngolaryngeal pain, throat irritation. Unknown frequency: pulmonary hypertension, wheezing.

Gastrointestinal Disorders: Common: pancreatitis, abdominal discomfort, abdominal distension, dysgeusia, flatulence. Uncommon: gastrointestinal hemorrhage, melena, mouth ulceration, gastroesophageal reflux, stomatitis, esophageal pain, dry mouth, gastritis, sensitivity of teeth. Unknown frequency: gastrointestinal ulcer perforation, retroperitoneal hemorrhage, hematemesis, gastric ulcer, esophagitis ulcerative, subileus, enterocolitis, hemorrhoids, hiatus hernia, rectal hemorrhage, gingivitis.

Hepatobiliary Disorders: Very common: hyperbilirubinemia. Common: hepatic function abnormal.

Uncommon: hepatotoxicity, toxic hepatitis, jaundice. Unknown frequency: cholestasis, hepatomegaly.

Skin and Subcutaneous Tissue Disorders: Common: eczema, urticaria, erythema, hyperhidrosis, contusion, and acne, dermatitis (including allergic, exfoliative and acneiform). Uncommon: exfoliative rash, drug eruption, pain of skin, ecchymosis. Unknown frequency: psoriasis, erythema multiforme, erythema nodosum, skin ulcer, palmar-plantar erythrodysesthesia syndrome, petechiae, photosensitivity, blister, dermal cyst, sebaceous hyperplasia, skin atrophy, skin discoloration, skin exfoliation, skin hyperpigmentation, skin hypertrophy, hyperkeratosis.

140mm

210mm

Musculoskeletal and Connective Tissue Disorders: Common: bone pain, musculoskeletal chest pain, musculoskeletal pain, back pain, neck pain, flank pain, muscular weakness. Uncommon: musculoskeletal stiffness, joint swelling. Unknown frequency: arthritis.

Renal and Urinary Disorders: Common: pollakiuria. Uncommon: dysuria, micturition urgency, nocturia.

Unknown frequency: renal failure, hematuria, urinary incontinence, chromaturia.

Reproductive System and Breast Disorders: Uncommon: breast pain, gynecomastia, erectile dysfunction.

Unknown frequency: breast induration, menorrhagia, nipple swelling.

General Disorders and Administration Site Conditions: Common: pyrexia, chest pain (including non-cardiac chest pain), pain, chest discomfort, malaise. Uncommon: gravitational edema, influenza-like illness, chills, feeling body temperature change (including feeling hot, feeling cold). Unknown frequency: localized edema.

Investigations: Very common: alanine aminotransferase increased, aspartate aminotransferase increased, lipase increased, lipoprotein cholesterol (including very low density and high density) increased, total cholesterol increased, blood triglycerides increased. Common: hemoglobin decreased, blood amylase increased, gammaglutamyltransferase increased, blood creatinine phosphokinase increased, blood alkaline phosphatase increased, weight decreased, weight increased, globulins decreased. Uncommon: blood lactate dehydrogenase increased, blood urea increased. Unknown frequency: troponin increased, blood bilirubin unconjugated increased, insulin C-peptide decreased, blood parathyroid hormone increased.

DRUG INTERACTIONS

Effects of Nilotinib on Drug Metabolizing Enzymes and Drug Transport Systems

Nilotinib is a competitive inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2D6 and UGT1A1 in vitro, potentially increasing the concentrations of drugs eliminated by these enzymes. In vitro studies also suggest that nilotinib may induce CYP2B6, CYP2C8 and CYP2C9, and decrease the concentrations of drugs which are eliminated by these enzymes.

In patients with CML, multiple doses of Nitonib increased the systemic exposure of oral midazolam (a substrate of CYP3A4) 2.6-fold. Nitonib is a moderate CYP3A4 inhibitor. As a result, the systemic exposure of drugs metabolized by CYP3A4 (e.g., certain HMG-CoA reductase inhibitors) may be increased when co-administered with Nitonib. Dose adjustment may be necessary for drugs that are CYP3A4 substrates, especially those that have narrow therapeutic indices (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, sirolimus and tacrolimus) when co-administered with Nitonib.

Single-dose administration of Nitonib to healthy subjects did not change the pharmacokinetics and pharmacodynamics of warfarin (a CYP2C9 substrate). The ability of multiple doses of Nitonib to induce metabolism of drugs other than midazolam has not been determined in vivo. Monitor patients closely when co-administering Nitonib with drugs that have a narrow therapeutic index and are substrates for CYP2B6, CYP2C8, or CYP2C9 enzymes.

Nilotinib inhibits human P-glycoprotein (P-gp). If Nitonib is administered with drugs that are substrates of Pgp, increased concentrations of the substrate drug are likely, and caution should be exercised.

Drugs that Inhibit or Induce Cytochrome P450 3A4 Enzymes

Nilotinib undergoes metabolism by CYP3A4, and concomitant administration of strong inhibitors or inducers of CYP3A4 can increase or decrease nilotinib concentrations significantly. Avoid the administration of Nitonib with agents that are strong CYP3A4 inhibitors. Concomitant use of Nitonib with medicinal products and herbal preparations that are potent inducers of CYP3A4 is likely to reduce exposure to nilotinib to a clinically relevant extent. Therefore, in patients receiving Nitonib, select alternative therapeutic agents with less potential for CYP3A4 induction for concomitant use.

Ketoconazole: In healthy subjects receiving ketoconazole, a CYP3A4 inhibitor, at 400 mg once daily for 6 days, systemic exposure (AUC) to nilotinib was increased approximately 3-fold.

Rifampicin: In healthy subjects receiving the CYP3A4 inducer, rifampicin, at 600 mg daily for 12 days, systemic exposure (AUC) to nilotinib was decreased approximately 80%.

Drugs that Affect Gastric pH

The concomitant use of proton pump inhibitors with Nitonib is not recommended. Nilotinib has pH-dependent solubility, with decreased solubility at higher pH. Drugs such as proton pump inhibitors that inhibit gastric acid secretion to elevate the gastric pH may decrease the solubility of nilotinib and reduce its bioavailability. In healthy subjects, co-administration of a single 400 mg dose of Nitonib with multiple doses of esomeprazole (a proton-pump inhibitor) at 40 mg daily decreased the nilotinib AUC by 34%. Increasing the dose of Nitonib when co-administered with such agents is not likely to compensate for the loss of exposure. Since proton pump inhibitors affect pH of the upper GI tract for an extended period, separation of doses may not eliminate the interaction.

In healthy subjects, no significant change in nilotinib pharmacokinetics was observed when a single 400 mg dose of Nitonib was administered 10 hours after and 2 hours before famotidine (an H2 blocker). Therefore, when the concurrent use of a H2 blocker is necessary, it may be administered approximately 10 hours before and approximately 2 hours after the dose of Nitonib.

Administration of an antacid (aluminum hydroxide/magnesium hydroxide/simethicone) to healthy subjects, 2 hours before or 2 hours after a single 400 mg dose of Nitonib did not alter nilotinib pharmacokinetics.

Therefore, if necessary, an antacid may be administered approximately 2 hours before or approximately 2 hours after the dose of Nitonib.

Drugs that Inhibit Drug Transport Systems

Nilotinib is a substrate of the efflux transporter P-glycoprotein (P-gp, ABCB1). If Nitonib is administered with drugs that inhibit P-gp, increased concentrations of nilotinib are likely, and caution should be exercised.

Drugs that May Prolong the QT Interval

The administration of Nitonib with agents that may prolong the QT interval such as anti-arrhythmic medicines should be avoided.

FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Risk Summary

Based on findings from animal studies and the mechanism of action, Nitonib 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. 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 Nitonib and for at least 14 days after the last dose.

Females and Males of Reproductive Potential

Pregnancy

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

Contraception

Females

Based on animal studies, Nitonib can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with Nitonib 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.

OVERDOSE

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

CONTRAINDICATIONS

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

STORAGE & INSTRUCTIONS

Store between 15°C to 25°C.

Protect from heat, sunlight and moisture.

Keep away from the reach of children.

To be sold on the prescription of a registered oncologist or on demand from cancer hospitals and institutions only.

HOW SUPPLIED

Nitonib Capsule 150mg

120 Capsules.

Nitonib Capsule 200mg

112 Capsules.

خوراک وطریقہ استعمال:

سرطان کے ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:

دوا کو ۱۵-۲۵ ڈگری سینٹی گریڈ درجہ حرارت کے درمیان رکھیں۔

دھوپ، گرمی، نمی سے محفوظ اور بچوں کی پہنچ سے دور رکھیں۔

صرف مستند اونکولوجسٹ یا کینسر ہسپتال کے نسخہ پر فروخت کریں۔

Manufactured by:

PHARMASOL

PRIVATE LIMITED

Plot # 549,Sundar Industrial Estate,
Lahore, Pakistan.