Rx **NILOTINIB**

NILTIB

150 mg and 200 mg Capsule
Antineoplastic Agent
(BCR-ABL tyrosine kinase inhibitor)

Formulation:
Each Capsule contains: Nilotinib Hydrochloride Dihydrate equivalent to Nilotinib 150 mg.
Each Capsule contains: Nilotinib Hydrochloride Dihydrate equivalent to Nilotinib 200 mg.

Description:
Nilotinib capsules 150mg:- Opaque Red cap & Opaque red body size '1' Hard gelatin capsules imprinted with 'H' on cap and '23' on body, filled with slightly yellow to yellowish granular powder.
Nilotinib capsules 200mg:- Opaque yellow cap & yellow body size '0' Hard gelatin capsules imprinted with 'H' on cap and '24' on body, filled with slightly yellow to yellowish granular powder.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Nilotinib capsules safely and effectively. See full prescribing information for Nilotinib capsules .

Nilotinib capsules for oral use
WARNING: QT PROLONGATION and SUDDEN DEATHS
See full prescribing information for complete boxed warning.

- **Nilotinib prolongs the QT interval. Prior to Nilotinib administration and periodically, monitor for hypokalemia or hypomagnesemia and correct deficiencies (5.2). Obtain ECGs to monitor the QTc at baseline, seven days after initiation, and periodically thereafter, and following any dose adjustments (5.2, 5.3, 5.7, 5.15).**
- **Sudden deaths have been reported in patients receiving nilotinib (5.3). Do not administer Nilotinib to patients with hypokalemia, hypomagnesemia, or long QT syndrome (4, 5.2).**
- **Avoid use of concomitant drugs known to prolong the QT interval and strong CYP3A4 inhibitors (5.8).**
- **Avoid food 2 hours before and 1 hour after taking the dose (5.9).**

----------**INDICATIONS AND USAGE**----------
Nilotinib is a kinase inhibitor indicated for:
The treatment of newly diagnosed adult patients with Philadelphia chromosome positive chronic myelogenous leukemia (Ph+ CML) in chronic phase. (1.1)
The treatment of chronic phase (CP) and accelerated phase (AP) Ph+ CML in adult patients resistant to or intolerant to prior therapy that included imatinib. (1.2)
----------**DOSAGE AND ADMINISTRATION**----------

- Recommended Dose: Newly diagnosed Ph+ CML-CP: 300 mg orally twice daily. Resistant or intolerant Ph+ CML-CP and CML-AP: 400 mg orally twice daily. (2.1)
- Take each Nilotinib dose approximately 12 hours apart. Nilotinib must be taken on an empty stomach. Avoid food for at least 2 hours before the dose is taken and avoid food for at least 1 hour after the dose is taken. (2.1)
- Swallow the capsules whole with water. (2.1)
- Dose adjustment may be required for hematologic and non-hematologic toxicities, and drug interactions. (2.2)
- A lower starting dose is recommended in patients with hepatic impairment (at baseline). (2.2)

----------**DOSAGE FORMS AND STRENGTHS**----------
150 mg and 200 mg hard capsules (3)
----------**CONTRAINDICATIONS**----------
Do not use in patients with hypokalemia, hypomagnesemia, or long QT syndrome. (4)
----------**WARNINGS AND PRECAUTIONS**----------

- Myelosuppression: Associated with neutropenia, thrombocytopenia and anemia. CBC should be done every 2 weeks for the first 2 months, then monthly. Reversible by withholding dose. Dose reduction may be required. (5.1)
- Cardiac and Arterial Vascular Occlusive Events: Cardiovascular events including ischemic heart disease, peripheral arterial occlusive disease and ischemic cerebrovascular events have been reported in patients with newly diagnosed Ph+ CML receiving Nilotinib. Cardiovascular status should be evaluated and cardiovascular risk factors monitored and managed during Nilotinib therapy. (5.4)
- Pancreatitis and elevated serum lipase: Monitor serum lipase monthly or as clinically indicated. In case lipase elevations are accompanied by abdominal symptoms, interrupt doses and consider appropriate diagnostics to exclude pancreatitis. (5.5)
- Hepatotoxicity: Nilotinib may result in elevations in bilirubin, AST/ALT, and alkaline phosphatase. Monitor hepatic function tests monthly or as clinically indicated. (5.6)
- Electrolyte abnormalities: Nilotinib can cause hypophosphatemia, hypokalemia, hyperkalemia, hypocalcemia, and hyponatremia. Correct electrolyte abnormalities prior to initiating Nilotinib and monitor periodically during therapy. (5.7, 5.15)
- Tumor lysis syndrome: Tumor lysis syndrome cases have been reported in Nilotinib treated patients with resistant or intolerant CML. Due to potential for tumor lysis syndrome, maintain adequate hydration and correct uric acid levels prior to initiating therapy with Nilotinib. (5.11)
- Hemorrhage: Hemorrhage from various sites was reported in patients with newly diagnosed CML and observed in the postmarketing reports of patients receiving Nilotinib therapy. (5.12)
- Drug interactions: Avoid concomitant use of strong inhibitors or inducers of CYP3A4. If patients must be coadministered a strong CYP3A4 inhibitor, dose reduction should be considered and the QT interval should be monitored closely. (5.8)
- Total gastrectomy: More frequent follow-up of these patients should be considered. If necessary, dose increase may be considered. (5.13)
- Embryo-fetal toxicity: Fetal harm can occur when administered to a pregnant woman. Women should be advised not to become pregnant when taking Nilotinib. (5.16)
- Fluid retention: Pericardial effusion, pleural effusion, and severe fluid retention have occurred in patients receiving Nilotinib. Monitor patients for signs and symptoms such as unexpected rapid weight gain, swelling, and shortness of breath. (5.17)

----------**ADVERSE REACTIONS**----------
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. (6.1)
----------**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 (7.1)
- CYP3A4 inhibitors may affect serum concentration (7.2)
- CYP3A4 inducers may affect serum concentration (7.2)

----------**USE IN SPECIFIC POPULATIONS**----------

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FULL PRESCRIBING INFORMATIONWARNING: QT PROLONGATION and SUDDEN DEATHS

See full prescribing information for complete boxed warning.

- **Nilotinib prolongs the QT interval. Prior to Nilotinib administration and periodically, monitor for hypokalemia or hypomagnesemia and correct deficiencies (5.2). Obtain ECGs to monitor the QTc at baseline, seven days after initiation, and periodically thereafter, and following any dose adjustments (5.2, 5.3, 5.7, 5.15).**
- **Sudden deaths have been reported in patients receiving nilotinib (5.3). Do not administer Nilotinib to patients with hypokalemia, hypomagnesemia, or long QT syndrome (4, 5.2).**
- **Avoid use of concomitant drugs known to prolong the QT interval and strong CYP3A4 inhibitors (5.8).**
- **Avoid food 2 hours before and 1 hour after taking the dose (5.9).**

1. INDICATIONS AND USAGE
1.1 Newly Diagnosed Ph+ CML-CP
Nilotinib (Niltib) is indicated for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukemia (Ph+ CML) in chronic phase. The effectiveness of Nilotinib is based on major molecular response and cytogenetic response rates
1.2 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.

2. DOSAGE AND ADMINISTRATION
2.1 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.
Newly Diagnosed Ph+ CML-CP
The recommended dose of Nilotinib is 300 mg orally twice daily.
Resistant or Intolerant Ph+ CML-CP and CML-AP
The recommended dose of Nilotinib is 400 mg orally twice daily.
2.2 Dose Adjustments or Modifications
QT Interval Prolongation:

ECGs with a QTc greater than 480 msec	1. Withhold Nilotinib, 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. If, following dose-reduction to 400 mg once daily, QTcF returns to greater than 480 msec, Nilotinib should be discontinued. 5. An ECG should be repeated approximately 7 days after any dose adjustment.

Myelosuppression
Withhold or dose-reduce Nilotinib 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 Nilotinib, 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 Nilotinib, 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 bilirubin greater than or equal to Grade 3	1. Withhold Nilotinib, and monitor bilirubin 2. Resume treatment at 400 mg once daily if bilirubin returns to less than or equal to Grade 1
Elevated hepatic transaminases greater than or equal to Grade 3	1. Withhold Nilotinib, 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 Nilotinib 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 Nilotinib should be interrupted. If patients must be coadministered 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 Nilotinib 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 [see Boxed Warning, Warnings and Precautions (5.2, 5.8), Drug Interactions (7.2)].
Concomitant Strong CYP3A4 Inducers
Avoid the concomitant use of strong CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital). Also inform patients not to take St. John's Wort since these agents may reduce the concentration of Nilotinib. Based on the nonlinear pharmacokinetic profile of Nilotinib, increasing the dose of Nilotinib when coadministered with such agents is unlikely to compensate for the loss of exposure.

3. DOSAGE FORMS AND STRENGTHS
Nilotinib capsules 150 mg:-
Nilotinib capsules are supplied as Hard gelatin capsule contains Nilotinib Hydrochloride dihydrate equivalent to Nilotinib 150mg.
Nilotinib capsules 200 mg:-
Nilotinib capsules are supplied as Hard gelatin capsule contains Nilotinib Hydrochloride dihydrate equivalent to Nilotinib 200mg.
Nilotinib capsules 150 mg:-
Opaque Red cap & Opaque red body size '1' Hard gelatin capsules imprinted with 'H' on cap and '23' on body, filled with slightly yellow to yellowish granular powder.
Nilotinib capsules 200 mg:-
Opaque yellow cap & yellow body size '0' Hard gelatin capsules imprinted with 'H' on cap and '24' on body, filled with slightly yellow to yellowish granular powder.

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

5. WARNINGS AND PRECAUTIONS
5.1 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 [see Dosage and Administration (2.2)].
5.2 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 [see Adverse Reactions (6.1), Clinical Pharmacology (12.6)]. 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 [see Warnings and Precautions (5.15)].
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 [see Warnings and Precautions (5.15)].
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 [see Warnings and Precautions (5.8, 5.9)]. The presence of hypokalemia and hypomagnesemia may further prolong the QT interval [see Warnings and Precautions (5.7, 5.15)].
5.3 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.
5.4 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 Nilotinib 300 and 400 mg bid 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 bid 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 bid 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 bid 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 *[see Dosage and Administration (2.2)]*.
5.5 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.
5.6 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 *[see Warnings and Precautions (5.15)]*.
5.7 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 *[see Warnings and Precautions (5.15)]*.
5.8 Drug Interactions
Avoid administration of Nilotinib 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 Nilotinib. If interruption of treatment with Nilotinib 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 *[see Boxed Warning, Dosage and Administration (2.2), Drug Interactions (7.2)]*.
5.9 Food Effects
The bioavailability of Nilotinib is increased with food, thus Nilotinib 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 *[see Boxed Warning, Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.
5.10 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 *[see Dosage and Administration (2.2) and Use in Specific Populations (8.7)]*.
5.11 Tumor Lysis Syndrome
Tumor lysis syndrome cases have been reported in Nilotinib 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 Nilotinib.
5.12 Hemorrhage
In a randomized trial in patients with newly diagnosed Ph+ CML in chronic phase comparing Nilotinib and imatinib, Grade 3 or 4 hemorrhage occurred in 1.1% of patients in the Nilotinib 300 mg bid arm, in 1.8% patients in the Nilotinib 400 mg bid arm, and 0.4% of patients in the imatinib arm. GI hemorrhage occurred in 2.9% and 5.1% of patients in the Nilotinib 300 mg bid and 400 mg bid 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 Nilotinib 300 mg bid and 400 mg bid arms, respectively, and in no patients in the imatinib arm.
5.13 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 *[see Clinical Pharmacology (12.3)]*.
5.14 Lactose
Since the capsules contain lactose, Nilotinib 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.
5.15 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 *[see Warnings and Precautions (5.2)]*. Monitor lipid profiles and glucose periodically during the first year of Nilotinib 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 *[see Drug Interactions (7.1)]*. Assess glucose levels before initiating treatment with Nilotinib and monitor during treatment as clinically indicated. If test results warrant therapy, physician should follow their local standards of practice and treatment guidelines.
5.16 Embryo-Fetal Toxicity
There are no adequate and well controlled studies of Nilotinib in pregnant women. However, Nilotinib may cause fetal harm when administered to a pregnant woman. Nilotinib caused embryo-fetal toxicities in animals at maternal exposures that were lower than the expected human exposure at the recommended doses of Nilotinib. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of child-bearing potential should avoid becoming pregnant while taking Nilotinib *[see Use in Specific Populations (8.1)]*.
5.17 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 Nilotinib 300 mg bid and 400 mg bid, 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 Nilotinib 300 mg bid and 400 mg bid, 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 Nilotinib 300 mg bid and 400 mg bid, 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 Nilotinib treatment; evaluate etiology and treat patients accordingly.

6. ADVERSE REACTIONS
The following serious adverse reactions can occur with Nilotinib and are discussed in greater detail in other sections of the package insert [see Boxed Warning, Warnings and Precautions (5)].

- Myelosuppression [see Warnings and Precautions (5.1)]
- QT Prolongation [see Boxed Warning, Warnings and Precautions (5.2)]
- Sudden Deaths [see Boxed Warning, Warnings and Precautions (5.3)]
- Cardiac and Arterial Vascular Occlusive Events [see Warnings and Precautions (5.4)]
- Pancreatitis and Elevated Serum Lipase [see Warnings and Precautions (5.5)]
- Hepatotoxicity [see Warnings and Precautions (5.6)]
- Electrolyte Abnormalities [see Boxed Warning, Warnings and Precautions (5.7)]
- Hemorrhage [see Warnings and Precautions (5.12)]
- Fluid Retention [see Warnings and Precautions (5.17)]

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
In Patients with Newly Diagnosed Ph+ CML-CP
The data below reflect exposure to Nilotinib from a randomized trial in patients with newly diagnosed Ph+ CML in chronic phase treated at the recommended dose of 300 mg twice daily (n=279). The median time on treatment in the Nilotinib 300 mg twice daily group was 61 months (range 0.1 to 71 months). The median actual dose intensity was 593 mg/day in the Nilotinib 300 mg twice daily group.
The most common (greater than 10%) non-hematologic adverse drug reactions were rash, pruritus, headache, nausea, fatigue, alopecia, myalgia, and upper abdominal pain. Constipation, diarrhea, dry skin, muscle spasms, arthralgia, abdominal pain, peripheral edema, vomiting, and asthenia were observed less commonly (less than or equal to 10% and greater than 5%) and have been of mild to moderate severity, manageable and generally did not require dose reduction.
Increase in QTcF greater than 60 msec from baseline was observed in 1 patient (0.4%) in the 300 mg twice daily treatment group. No patient had an absolute QTcF of greater than 500 msec while on study drug.
The most common hematologic adverse drug reactions (all grades) were myelosuppression including: thrombocytopenia (18%), neutropenia (15%) and anemia (8%). See Table 7 for Grade 3/4 laboratory abnormalities.
Discontinuation due to adverse reactions, regardless of relationship to study drug, was observed in 10% of patients.
In Patients with Resistant or Intolerant Ph+ CML-CP and CML-AP
In the single open-label multicenter clinical trial, a total of 458 patients with Ph+ CML-CP and CML-AP resistant to or intolerant to at least one prior therapy including imatinib were treated (CML-CP=321; CMLAP=137) at the recommended dose of 400 mg twice daily.
The median duration of exposure in days for CML-CP and CML-AP patients is 561 (range 1 to 1096) and 264 (range 2 to 1160), respectively. The median dose intensity for patients with CML-CP and CML-AP is 789 mg/day (range 151 to 1110) and 780 mg/day (range 150 to 1149), respectively and corresponded to the planned 400 mg twice daily dosing.
The median cumulative duration in days of dose interruptions for the CML-CP patients was 20 (range 1 to 345), and the median duration in days of dose interruptions for the CML-AP patients was 23 (range 1 to 234).
In patients with CML-CP, the most commonly reported non-hematologic adverse drug reactions (greater than or equal to 10%) were rash, pruritus, nausea, fatigue, headache, constipation, diarrhea, vomiting and myalgia. The common serious drug-related adverse reactions (greater than or equal to 1% and less than 10%) were thrombocytopenia, neutropenia and anemia.
In patients with CML-AP, the most commonly reported non-hematologic adverse drug reactions (greater than or equal to 10%) were rash, pruritus and fatigue. The common serious adverse drug reactions (greater than or equal to 1% and less than 10%) were thrombocytopenia, neutropenia, febrile neutropenia, pneumonia, leukopenia, intracranial hemorrhage, elevated lipase and pyrexia.
Sudden deaths and QT prolongation were reported. The maximum mean QTcF change from baseline at steady-state was 10 msec. Increase in QTcF greater than 60 msec from baseline was observed in 4.1% of the patients and QTcF of greater than 500 msec was observed in 4 patients (less than 1%) *(see Boxed Warning, Warnings and Precautions (5.2, 5.3), Clinical Pharmacology (12.6)]*.
Discontinuation due to adverse drug reactions was observed in 16% of CML-CP and 10% of CML-AP patients.
Most Frequently Reported Adverse Reactions
Tables 5 and 6 show the percentage of patients experiencing non-hematologic adverse reactions (excluding laboratory abnormalities) regardless of relationship to study drug. Adverse reactions reported in greater than 10% of patients who received at least 1 dose of Nilotinib are listed.

Table 5: Most Frequently Reported Non-hematologic Adverse Reactions (Regardless of Relationship to Study Drug) in Patients with Newly Diagnosed Ph+<1ML-CP (Greater than or equal to 10% in Nilotinib 300 mg Twice Daily or Imatinib 400 mg Once Daily Groups) 60-Month Analysis[a]

		Patients with Newly Diagnosed Ph+ CML-CP			
		NILOTINIB	Imatinib	NILOTINIB	Imatinib
		300 mg twice daily	400 mg once daily	300 mg twice daily	400 mg once daily
		N=279	N=280	N=279	N=280
Body System and Preferred Term		All Grades (%)		CTC Gradesb 3/4 (%)	
Skin and subcutaneous tissue disorders	Rash	38	19	<1	2
	Pruritus	21	7	<1	0
	Alopecia	13	7	0	0
	Dry skin	12	6	0	0
Gastrointestinal disorders	Nausea	22	41	2	2
	Constipation	20	8	<1	0
	Diarrhea	19	46	1	4
	Vomiting	15	27	<1	<1
	Abdominal pain upper	18	14	1	<1
	Abdominal pain	15	12	2	0
	Dyspepsia	20	12	0	0
Nervous system disorders	Headache	32	23	3	<1
	Dizziness	12	11	<1	<1
General disorders and administration site conditions	Fatigue	23	20	1	1
	Pyrexia	14	13	<1	0
	Asthenia	14	12	<1	0
	Peripheral edema	9	20	<1	0
	Face edema	<1	14	0	<1
Musculoskeletal and connective tissue disorders	Myalgia	19	19	<1	<1
	Arthralgia	22	17	<1	<1
	Muscle spasms	12	34	0	1
	Pain in extremity	15	16	<1	<1
	Back pain	19	17	1	1
Respiratory, thoracic and mediastinal disorders	Cough	17	13	0	0
	Oropharyngeal pain	12	6	0	0
	Dyspnea	11	6	2	<1
Infections and infestations	Nasopharyngitis	27	21	0	0
	Upper respiratory tractinfection	17	14	<1	0
	Influenza	13	9	0	0
	Gastroenteritis	7	10	0	<1
Eye disorders	Eyelid edema	1	19	0	0
	Periorbital edema	<1	15	0	0
Psychiatric disorders	Insomnia	11	9	0	0
Vascular disorder	Hypertension	10	4	1	<1

[a]Excluding laboratory abnormalities
[b]NCI Common Terminology Criteria for Adverse Events, Version 3.0

Table 6: Most Frequently Reported Non-hematologic Adverse Reactions in Patients with Resistant or Intolerant Ph+ CML Receiving Nilotinib 400 mg Twice Daily (Regardless of Relationship to Study Drug) (Greater than or equal to 10% in any Group) 24-Month Analysis[a]

		CML-CP		CML-AP	
		N=321		N=137	
Body System and Preferred Term		All Grades (%)	CTC Grades[b] 3/4 (%)	All Grades (%)	CTC Gradesb 3/4 (%)
Skin and subcutaneous tissue disorders	Rash	36	2	29	0
	Pruritus	32	<1	20	0
	Night sweat	12	<1	27	0
	Alopecia	11	0	12	0
Gastrointestinal disorders	Nausea	37	1	22	<1
	Constipation	26	<1	19	0
	Diarrhea	28	3	24	2
	Vomiting	29	<1	13	0
	Abdominal pain	15	2	16	3
	Abdominal pain upper	14	<1	12	<1
	Dyspepsia	10	<1	4	0

Size: 350 x 550 mm
Colour: Black

		CML-CP		CML-AP	
		N=321		N=137	
Body System and Preferred Term		**All Grades (%)**	**CTC Grades[b] 3/4 (%)**	**All Grades (%)**	**CTC Gradesb 3/4 (%)**
Nervous system disorders	Headache	35	2	20	1
General disorders and administration site conditions	Fatigue	32	3	23	<1
	Pyrexia	22	<1	28	2
	Asthenia	16	0	14	1
	Peripheral edema	15	<1	12	0
Musculoskeletal and connective tissue disorders	Myalgia	19	2	16	<1
	Arthralgia	26	2	16	0
	Muscle spasms	13	<1	15	0
	Bone pain	14	<1	15	2
	Pain in extremity	20	2	18	1
	Back pain	17	2	15	<1
	Musculoskeletal pain	11	<1	12	1
Respiratory, thoracic and mediastinal disorders	Cough	27	<1	18	0
	Dyspnea	15	2	9	2
	Oropharyngeal pain	11	0	7	0
Infections and infestations	Nasopharyngitis	24	<1	15	0
	Upper respiratory tract infection	12	0	10	0
Metabolism and nutrition disorders	Decreased appetitec	15	<1	17	<1
Psychiatric disorders	Insomnia	12	1	7	0
Vascular disorders	Hypertension	10	2	11	<1

[a]Excluding laboratory abnormalities [b]NCI Common Terminology Criteria for Adverse Events, Version 3.0 [c]Also includes preferred term anorexia

Laboratory Abnormalities

Table 7 shows the percentage of patients experiencing treatment-emergent Grade 3/4 laboratory abnormalities in patients who received at least one dose of Nilotinib.

Table 7: Percent Incidence of Clinically Relevant Grade 3/4* Laboratory Abnormalities

	Patient Population			
			Resistant or Intolerant Ph+	
	Newly Diagnosed Ph+ CML-CP			
			CML-CP	CML-AP
	NILOTINIB 300 mg	Imatinib 400 mg	NILOTINIB 400 mg	NILOTINIB 400 mg
	twice daily N=279 (%)	once daily N=280 (%)	twice daily N=321 (%)	twice daily N=137 (%)
Hematologic Parameters				
Thrombocytopenia	10	9	30[1]	42[3]
Neutropenia	12	22	31[2]	42[4]
Anemia	4	6	11	27
Biochemistry Parameters				
Elevated lipase	9	4	18	18
Hyperglycemia	7	<1	12	6
Hypophosphatemia	8	10	17	15
Elevated bilirubin (total)	4	<1	7	9
Elevated SGPT (ALT)	4	3	4	4
Hyperkalemia	2	1	6	4
Hyponatremia	1	<1	7	7
Hypokalemia	<1	2	2	9
Elevated SGOT (AST)	1	1	3	2
Decreased albumin	0	<1	4	3
Hypocalcemia	<1	<1	2	5
Elevated alkaline phosphatase	0	<1	<1	1
Elevated creatinine	0	<1	<1	<1

*NCI Common Terminology Criteria for Adverse Events, version 3.0
[1]CML-CP: Thrombocytopenia: 12% were Grade 3, 18% were Grade 4
[2]CML-CP: Neutropenia: 16% were Grade 3, 15% were Grade 4
[3]CML-AP: Thrombocytopenia: 11% were Grade 3, 32% were Grade 4
[4]CML-AP: Neutropenia: 16% were Grade 3, 26% were Grade 4

Elevated total cholesterol (all grades) occurred in 28% (Nilotinib 300 mg bid) and 4% (imatinib). Elevated triglycerides (all grades) occurred in12% and 8% of patients in the Nilotinib and imatinib arms, respectively. Hyperglycemia (all grades) occurred in 50% and 31% of patients in the Nilotinib and imatinib arms, respectively.
Most common biochemistry laboratory abnormalities (all grades) were alanine aminotransferase increased (72%), blood bilirubin increased (59%), aspartate aminotransferase increased (47%), lipase increased (28%), blood glucose increased (50%), blood cholesterol increased (28%), and blood triglyceride increased (12%).

Additional Data from Clinical Trials

The following adverse drug reactions were reported in patients in the Nilotinib 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%), which were not included in Tables 5 and 6, 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, 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: papilloedema, 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, 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, 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.
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.

7. DRUG INTERACTIONS

7.1 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 Nilotinib increased the systemic exposure of oral midazolam (a substrate of CYP3A4) 2.6-fold. Nilotinib 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 coadministered with Nilotinib. 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 coadministered with Nilotinib.

Single-dose administration of Nilotinib to healthy subjects did not change the pharmacokinetics and pharmacodynamics of warfarin (a CYP2C9 substrate). The ability of multiple doses of Nilotinib to induce metabolism of drugs other than midazolam has not been determined in vivo. Monitor patients closely when coadministering Nilotinib 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 Nilotinib is administered with drugs that are substrates of Pgp, increased concentrations of the substrate drug are likely, and caution should be exercised.

7.2 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. The administration of Nilotinib with agents that are strong CYP3A4 inhibitors should be avoided [see Boxed Warning, Dosage and Administration (2.2), Warnings and Precautions (5.2, 5.8)]. Concomitant use of Nilotinib 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 Nilotinib, concomitant use of alternative therapeutic agents with less potential for CYP3A4 induction should be selected.

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%.

7.3 Drugs that Affect Gastric pH

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, coadministration of a single 400 mg dose of Nilotinib with multiple doses of esomeprazole (a proton pump inhibitor) at 40 mg daily decreased the Nilotinib AUC by 34%. Increasing the dose of Nilotinib when coadministered 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. The concomitant use of proton pump inhibitors with Nilotinib is not recommended.

In healthy subjects, no significant change in Nilotinib pharmacokinetics was observed when a single 400 mg dose of Nilotinib 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 Nilotinib.

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 Nilotinib 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 Nilotinib.

7.4 Drugs that Inhibit Drug Transport Systems

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

7.5 Drugs that May Prolong the QT Interval

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

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[see Warnings and Precautions (5.16)]*.

Risk Summary

Based on its mechanism of action and findings in animals, Nilotinib may cause fetal harm when administered to a pregnant woman. Women should be advised to avoid becoming pregnant while on Nilotinib. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

8.3 Nursing Mothers

It is not known whether Nilotinib is excreted in human milk. One study in lactating rats demonstrates that Nilotinib is excreted into milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Nilotinib, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

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

8.5 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.

8.6 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 *[see Boxed Warning, Warnings and Precautions (5.2)]*.

8.7 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 8 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 *[see Dosage and Administration (2.2), Warnings and Precautions (5.10)]*.

Table 8: Child-Pugh Liver Function Classification

Assessment	Degree of Abnormality	Score
Encephalopathy Grade	None	1
	1 or 2	2
	3 or 4	3
Ascites	Absent	1
	Slight	2
	Moderate	3
Total Bilirubin (mg/dL)	<2	1
	2–3	2
	>3	3
Serum Albumin (g/dL)	>3.5	1
	2.8–3.5	2
	<2.8	3
Prothrombin Time (seconds prolonged)	<4	1
	4–6	2
	>6	3

10. OVERDOSAGE

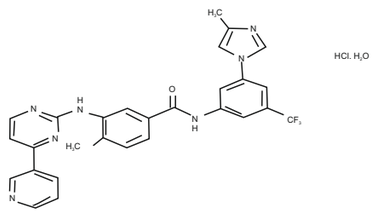
Overdose with Nilotinib has been reported, where an unspecified number of Nilotinib capsules were ingested in combination with alcohol and other drugs. Events included neutropenia, vomiting, and drowsiness. In the event of overdose, the patient should be observed and appropriate supportive treatment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

11. DESCRIPTION

Nilotinib (Nilotinib) belongs to a pharmacologic class of drugs known as kinase inhibitors.
Nilotinib drug substance, a monohydrate monohydrochloride, is a white to slightly yellowish to slightly greenish yellow powder with the anhydrous molecular formula and weight, respectively, of C28 H22 F3N7OHCl

- H2O and 584. The solubility of Nilotinib in aqueous solutions decreases with increasing pH. Nilotinib is not optically active. The pKa1 was determined to be 2.1; pKa2 was estimated to be 5.4.

The chemical name of Nilotinib is 4-methyl-N-[3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl]-3[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-benzamide, monohydrochloride, monohydrate. Its structure is shown below:



Nilotinib (Nilotinib) capsules, for oral use, contain 150 mg or 200 mg Nilotinib base, anhydrous (as hydrochloride, monohydrate) with the following inactive ingredients: colloidal silicon dioxide, crospovidone, lactose monohydrate, magnesium stearate and poloxamer 188. The capsules contain gelatin, iron oxide (red), iron oxide (yellow), iron oxide (black), and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 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).

12.3 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 *[see Warnings and Precautions (5.13)]*.

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.

12.5 Pharmacogenomics

Nilotinib can increase bilirubin levels. A pharmacogenetic analysis of 97 patients evaluated the polymorphisms of UGT1A1 and its potential association with hyperbilirubinemia during Nilotinib 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 *[see Warnings and Precautions (5.6)]*.

12.6 QT/QTc Prolongation

In a placebo-controlled study in healthy volunteers designed to assess the effects of Nilotinib on the QT interval, administration of Nilotinib 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 *[see Boxed Warning, Warnings and Precautions (5.2), and Adverse Reactions (6.1)]*.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A 2-year carcinogenicity study was conducted orally in rats at Nilotinib doses of 5, 15, and 40 mg/kg/day. Exposures in animals at the highest dose tested were approximately 2-to 3-fold the human exposure (based on AUC) at the Nilotinib dose of 400 mg twice daily. The study was negative for carcinogenic findings. A 26-week carcinogenicity study was conducted orally in Tg.rasH2 mice, a model genetically modified to enhance susceptibility to neoplastic transformation, at Nilotinib doses of 30, 100, and 300 mg/kg/day. Nilotinib induced in the skin and subcutis statistically significant increases in the incidence of papillomas in females and of papillomas and combined papillomas and carcinomas in males at 300 mg/kg/day. The no-observed-adverseeffect-level (NOAEL) for skin neoplastic lesions was 100 mg/kg/day.
Nilotinib was not mutagenic in a bacterial mutagenesis (Ames) assay, was not clastogenic in a chromosome aberration assay in human lymphocytes, did not induce DNA damage (comet assay) in L5178Y mouse lymphoma cells, nor was it clastogenic in an in vivo rat bone marrow micronucleus assay with two oral treatments at doses up to 2000 mg/kg/dose.
There were no effects on male or female rat and female rabbit mating or fertility at doses up to 180 mg/kg in rats (approximately 4-to 7-fold for males and females, respectively, the AUC in patients at the dose of 400 mg twice daily) or 300 mg/kg in rabbits (approximately one-half the AUC in patients at the dose of 400 mg twice daily). The effect of Nilotinib on human fertility is unknown. In a study where male and female rats were treated with Nilotinib at oral doses of 20 to 180 mg/kg/day (approximately 1-to 6.6-fold the AUC in patients at the dose of 400 mg twice daily) during the pre-mating and mating periods and then mated, and dosing of pregnant rats continued through gestation Day 6, Nilotinib increased post-implantation loss and early resorption, and decreased the number of viable fetuses and litter size at all doses tested.

14. CLINICAL STUDIES

14.1 Newly Diagnosed Ph+ CML-CP

An open-label, multicenter, randomized trial was conducted to determine the efficacy of Nilotinib versus imatinib tablets in adult patients with cytogenetically confirmed newly diagnosed Ph+ CML-CP. Patients were within 6 months of diagnosis and were previously untreated for CML-CP, except for hydroxyurea and/or anagrelide. Efficacy was based on a total of 846 patients: 283 patients in the imatinib 400 mg once daily group, 282 patients in the Nilotinib 300 mg twice daily group, 281 patients in the Nilotinib 400 mg twice daily group.
Median age was 46 years in the imatinib group and 47 years in both Nilotinib groups, with 12%, 13%, and 10% of patients greater than or equal to 65 years of age in imatinib 400 mg once daily, Nilotinib 300 mg twice daily and Nilotinib 400 mg twice daily treatment groups, respectively. There were slightly more male than female patients in all groups (56%, 56%, and 62% in imatinib 400 mg once daily, Nilotinib 300 mg twice daily and Nilotinib 400 mg twice daily treatment groups, respectively). More than 60% of all patients were Caucasian, and 25% were Asian.
The primary data analysis was performed when all 846 patients completed 12 months of treatment (or discontinued earlier). Subsequent analyses were done when patients completed 24, 36, 48, and 60 months of treatment (or discontinued earlier). The median time on treatment was approximately 61 months in all three treatment groups.
The primary efficacy endpoint was major molecular response (MMR) at 12 months after the start of study medication. MMR was defined as less than or equal to 0.1% BCR-ABL/ABL % by international scale measured by RQ-PCR, which corresponds to a greater than or equal to 3 log reduction of BCR-ABL transcript from standardized baseline. Efficacy endpoints are summarized in Table 9.
Two patients in the Nilotinib arm progressed to either accelerated phase or blast crisis (both within the first 6 months of treatment) while 12 patients on the imatinib arm progressed to either accelerated phase or blast crisis (7 patients within first 6 months, 2 patients within 6 to 12 months, 2 patients within 12 to 18 months and 1 patient within 18 to 24 months)

Table 9: Efficacy (MMR and CCyR) of NILOTINIB Compared to Imatinib in Newly Diagnosed Ph+ CML-CP

	NILOTINIB	Imatinib
	300 mg twice daily	400 mg once daily
	N=282	N=283
MMR at 12 months (95% CI)	44% (38.4, 50.3)	22% (17.6, 27.6)
P-Value[a]	<0.0001	
CCyR[b] by 12 months (95% CI)	80% (75.0, 84.6)	65% (59.2, 70.6)
MMR at 24 months (95% CI)	62% (55.8, 67.4)	38% (31.8, 43.4)
CCyR[b] by 24 months (95% CI)	87% (82.4, 90.6)	77% (71.7, 81.8)

[a]CMH test stratified by Sokal risk group
[b]CCyR: 0% Ph+ metaphases. Cytogenetic responses were based on the percentage of Ph-positive metaphases among greater than or equal to 20 metaphase cells in each bone marrow sample.
By the 60 months, MMR was achieved by 77% of patients on Nilotinib and 60% of patients on imatinib. Median overall survival was not reached in either arm. At the time of the 60-month final analysis, the estimated survival rate was 93.7% for patients on Nilotinib and 91.7% for patients on imatinib.

14.2 Patients with Resistant or Intolerant Ph+ CML-CP and CML-AP

A single-arm, open-label, multicenter study was conducted to evaluate the efficacy and safety of Nilotinib (400 mg twice daily) in patients with imatinib-resistant or -intolerant CML with separate cohorts for chronic and accelerated phase disease. The definition of imatinib resistance included failure to achieve a complete hematologic response (by 3 months), cytogenetic response (by 6 months) or major cytogenetic response (by 12 months) or progression of disease after a previous cytogenetic or hematologic response. Imatinib intolerance was defined as discontinuation of treatment due to toxicity and lack of a major cytogenetic response at time of study entry. At the time of data cut-off, 321 patients with CML-CP and 137 patients with CML-AP with a minimum follow-up of 24 months were enrolled. In this study, about 50% of CML-CP and CML-AP patients were males, over 90% (CML-CP) and 80% (CML-AP) were Caucasian, and approximately 30% were age 65 years or older.
Overall, 73% of patients were imatinib resistant while 27% were imatinib intolerant. The median time of prior imatinib treatment was approximately 32 (CML-CP) and 28 (CML-AP) months. Prior therapy included hydroxyurea in 85% of patients, interferon in 56% and stem cell or bone marrow transplant in 8%. The median highest prior imatinib dose was 600 mg per day for patients with CML-CP and CML-AP, and the highest prior imatinib dose was greater than or equal to 600 mg/day in 74% of all patients with 40% of patients receiving imatinib doses greater than or equal to 800 mg/day.
Median duration of Nilotinib treatment was 18.4 months in patients with CML-CP and 8.7 months in patients with CML-AP.
The efficacy endpoint in CML-CP was unconfirmed major cytogenetic response (MCyR) which included complete and partial cytogenetic responses.
The efficacy endpoint in CML-AP was confirmed hematologic response (HR), defined as either a complete hematologic response (CHR) or no evidence of leukemia (NEL). The rates of response for CML-CP and CMLAP patients are reported in Table 10. Median durations of response had not been reached at the time of data analysis.

Table 10: Efficacy of Nilotinib in Resistant or Intolerant Ph+ CML-CP and CML-AP

Cytogenetic Response Rate (Unconfirmed) (%)[a]	
	Chronic Phase (n=321)
Major (95% CI)	51% (46%–57%)
Complete (95% CI)	37% (32%–42%)
Partial (95% CI)	15% (11%–19%)
	Accelerated Phase (n=137)
Hematologic Response Rate (Confirmed) (95% CI)b	39% (31%–48%)
Complete Hematologic Response Rate (95% CI)	30% (22%–38%)
No Evidence of Leukemia (95% CI)	9% (5%–16%)

[a]Cytogenetic response criteria: Complete (0% Ph + metaphases) or partial (1% to 35%). Cytogenetic responses were based on the percentage of Ph-positive metaphases among greater than or equal to 20 metaphase cells in each bone marrow sample.
[b]Hematologic response=CHR + NEL (all responses confirmed after 4 weeks). CHR (CML-CP): WBC less than 10 x 10^9/L, platelets less than 450,000/mm^3, no blasts or promyelocytes in peripheral blood, less than 5% myelocytes + metamyelocytes in bone marrow, less than 20% basophils in peripheral blood, and no extramedullary involvement. CHR (CML-AP): neutrophils greater than or equal to 1.5 x 10^9/L, platelets greater than or equal to 100 x 10^9/L, no myeloblasts in peripheral blood, myeloblasts less than 5% in bone marrow, and no extramedullary involvement. NEL: same criteria as for CHR but neutrophils greater than or equal to 1.0 x 10^9/L and platelets greater than or equal to 20 x 10^9/L without transfusions or bleeding.

Patients with Chronic Phase

The MCyR rate in 321 CML-CP patients was 51%. The median time to MCyR among responders was 2.8 months (range 1 to 28 months). The median duration of MCyR cannot be estimated. The median duration of exposure on this single arm-trial was 18.4 months. Among the CML-CP patients who achieved MCyR, 62% of them had MCyR lasting more than 18 months. The CCyR rate was 37%.

Patients with Accelerated Phase

The overall confirmed hematologic response rate in 137 patients with CML-AP was 39%. The median time to first hematologic response among responders was 1 month (range 1 to 14 months). Among the CML-AP patients who achieved HR, 44% of them had a response lasting for more than 18 months.
After Imatinib failure, 24 different BCR-ABL mutations were noted in 42% of chronic phase and 54% of accelerated phase CML patients who were evaluated for mutations.

16. HOW SUPPLIED/STORAGE AND HANDLING

Nilotinib Capsules 150 mg are supplied in Blister Pack.
Nilotinib Capsules 200 mg are supplied in Blister Pack.
Storage: Store at temperatures not exceeding 30°C. Protect from moisture

17. PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).
A Medication Guide is required for distribution with Nilotinib. The complete text of the Medication Guide is reprinted at the end of this document.

Myelosuppression

Advise patients that treatment with Nilotinib can cause serious thrombocytopenia, neutropenia, and anemia. Advise patients to seek immediate medical attention if symptoms suggestive of low blood counts occur, such as fever, chills or other signs of infection, unexplained bleeding or bruising, or unexplained weakness or shortness of breath *[see Warnings and Precautions (5.1)]*.

QT Prolongation

Advise patients that Nilotinib can cause possibly life-threatening, abnormal heart beat. Advise patients to seek immediate medical attention if symptoms of abnormal heart beat occur, such as feeling lightheaded, faint or experiencing an irregular heartbeat *[see Warnings and Precautions (5.2)]*.

Cardiac and Arterial Vascular Occlusive Events

Advise patients that cardiovascular events (including ischemic heart disease, peripheral arterial occlusive disease, and ischemic cerebrovascular events) have been reported. Advise patients to seek immediate medical attention if any symptoms suggestive of a cardiovascular event occur, such as chest or leg pain, numbness or weakness, or problems walking or speaking occur suddenly *[see Warnings and Precautions (5.4)]*.

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