

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Tasigna safely and effectively. See full prescribing information for Tasigna.

Tasigna® (nilotinib) Capsules

Initial U.S. Approval: 2007

WARNING: QT PROLONGATION AND SUDDEN DEATHS

See full prescribing information for complete boxed warning.

- Tasigna prolongs the QT interval. Prior to Tasigna 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 follow any dose adjustments (5.2, 5.3, 5.6, 5.13).
- Sudden deaths have been reported in patients receiving nilotinib (5.3). Do not administer Tasigna 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 (5.7).
- Patients should avoid food 2 hours before and 1 hour after taking dose (5.8).

-----RECENT MAJOR CHANGES-----

Dosage and Administration: Recommended Dosing (2.1)	1/2011
Warnings and Precautions: Sudden Deaths (5.3),	
Food Effect (5.8)	1/2011
Warnings and Precautions: Tumor Lysis Syndrome (5.10)	10/2011

-----INDICATIONS AND USAGE-----

Tasigna is a kinase inhibitor indicated for:

The treatment of newly diagnosed adult patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase. The study is ongoing and further data will be required to determine long-term outcome. (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)
- Administer Tasigna approximately 12 hours apart and must not take with food. (2.1)
- Swallow the capsules whole with water. Do not consume food for at least 2 hours before the dose is taken and for at least one hour after. (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)
- QT Prolongation: Tasigna prolongs the QT interval. Correct hypokalemia or hypomagnesemia prior to administration and monitor periodically. (5.2) Avoid drugs known to prolong the QT interval and strong CYP3A4 inhibitors. (5.7) Use with caution in patients with hepatic impairment (5.9). Obtain ECGs at baseline, seven days after initiation, and periodically thereafter, as well as following any dose adjustments. (5.2, 5.3, 5.6, 5.13)

- Sudden deaths: Sudden deaths have been reported in patients with resistant or intolerant Ph+ CML receiving nilotinib. Ventricular repolarization abnormalities may have contributed to their occurrence.
- Elevated serum lipase: Check serum lipase periodically. In case lipase elevations are accompanied by abdominal symptoms, interrupt doses and consider appropriate diagnostics to exclude pancreatitis. Caution is recommended in patients with history of pancreatitis. (5.4)
- Liver function abnormality: Tasigna may result in elevations in bilirubin, AST/ALT, and alkaline phosphatase. Check hepatic function tests periodically. (5.5)
- Electrolyte abnormalities: Tasigna can cause hypophosphatemia, hypokalemia, hyperkalemia, hypocalcemia, and hyponatremia. Correct electrolyte abnormalities prior to initiating Tasigna and monitor periodically during therapy. (5.6, 5.13)
- Hepatic impairment: Nilotinib exposure is increased in patients with impaired hepatic function (at baseline). A dose reduction is recommended in these patients and QT interval should be monitored closely. (5.9)
- Tumor Lysis Syndrome: Cases of tumor lysis syndrome have been reported in Tasigna 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 Tasigna. (5.10)
- Drug interactions: Avoid concomitant use of strong inhibitors or inducers of CYP3A4. If patients must be co-administered a strong CYP3A4 inhibitor, dose reduction should be considered and the QT interval should be monitored closely. (5.7)
- Food Effects: Food increases blood levels of Tasigna.
- Avoid food 2 hours before and 1 hour after a dose. (5.8)
- Total gastrectomy: More frequent follow-up of these patients should be considered. If necessary, dose increase may be considered (5.11).
- Pregnancy: Fetal harm can occur when administered to a pregnant woman. Women should be advised not to become pregnant when taking Tasigna. (5.14, 8.1)

-----ADVERSE REACTIONS-----

The most commonly reported non-hematologic adverse reactions (≥10%) in patients with newly diagnosed Ph+ CML-CP, resistant or intolerant Ph+ CML-CP, or resistant or intolerant Ph+ CML-AP were rash, pruritus, headache, nausea, fatigue, myalgia, nasopharyngitis, constipation, diarrhea, abdominal pain, vomiting, arthralgia, pyrexia, upper respiratory tract infection, back pain, cough, and asthenia. Hematologic adverse drug reactions include myelosuppression: thrombocytopenia, neutropenia and anemia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----DRUG INTERACTIONS-----

- Tasigna is an inhibitor of CYP3A4, CYP2C8, CYP2C9, and CYP2D6. It may also induce CYP2B6, CYP2C8 and CYP2C9. Therefore, Tasigna 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-----

- Sexually active female patients should use effective contraception during treatment (8.1)
- Should not breast-feed (8.3)
- No data to support use in pediatrics (8.4)
- A lower starting dose is recommended in patients with hepatic impairment (at baseline). (2.2, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

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FULL PRESCRIBING INFORMATION: CONTENTS*
WARNING: QT PROLONGATION AND SUDDEN DEATHS

1 INDICATIONS AND USAGE

- 1.1 Newly Diagnosed Ph+ CML-CP
- 1.2 Resistant or Intolerant Ph+ CML-CP and CML-AP

2 DOSAGE AND ADMINISTRATION

- 2.1 Recommended Dosing
- 2.2 Dose Adjustments or Modifications

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Myelosuppression
- 5.2 QT Prolongation
- 5.3 Sudden Deaths
- 5.4 Elevated Serum Lipase
- 5.5 Hepatotoxicity
- 5.6 Electrolyte Abnormalities
- 5.7 Drug Interactions
- 5.8 Food Effects
- 5.9 Hepatic Impairment
- 5.10 Tumor Lysis Syndrome
- 5.11 Total Gastrectomy
- 5.12 Lactose
- 5.13 Monitoring Laboratory Tests
- 5.14 Use in Pregnancy

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Additional Data from Clinical Trials

7 DRUG INTERACTIONS

- 7.1 Effects of Nilotinib on Drug Metabolizing Enzymes and Drug Transport Systems
- 7.2 Drugs that Inhibit or Induce Cytochrome P450 3A4 Enzymes
- 7.3 Drugs that Affect Gastric pH

7.4 Drugs that Inhibit Drug Transport Systems

7.5 Drugs that May Prolong the QT Interval

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Cardiac Disorders
- 8.7 Hepatic Impairment
- 8.8 Renal Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics
- 12.4 QT/QTc Prolongation
- 12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

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

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

- 17.1 Taking Tasigna
- 17.2 Drug Interactions
- 17.3 Pregnancy
- 17.4 Compliance

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: QT PROLONGATION AND SUDDEN DEATHS

- Tasigna prolongs the QT interval. Prior to Tasigna 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 follow any dose adjustments (5.2, 5.3, 5.6, 5.13).
- Sudden deaths have been reported in patients receiving nilotinib (5.3). Do not administer Tasigna 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 (5.7).
- Patients should avoid food 2 hours before and 1 hour after taking dose (5.8).

1 INDICATIONS AND USAGE

1.1 Newly Diagnosed Ph+ CML-CP

Tasigna (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 Tasigna is based on major molecular response and cytogenetic response rates [see *Clinical Studies (14.1)*]. The study is ongoing and further data will be required to determine long-term outcome.

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

Tasigna 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 Tasigna is based on hematologic and cytogenetic response rates [see *Clinical Studies (14.2)*].

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

Tasigna should be taken twice daily at approximately 12 hour intervals and must not be taken with food. The capsules should be swallowed whole with water. No food should be consumed for at least 2 hours before the dose is taken and no food should be consumed for at least one hour after the dose is taken [see *Boxed Warning, Warnings and Precautions (5.8), Clinical Pharmacology (12.3)*].

For patients who are unable to swallow capsules, the contents of each capsule may be dispersed in one teaspoon of applesauce (puréed apple). The mixture should be taken immediately (within 15 minutes) and should not be stored for future use [see *Clinical Pharmacology (12.3)*].

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

Newly Diagnosed Ph+ CML-CP

The recommended dose of Tasigna is 300 mg orally twice daily [see *Clinical Pharmacology (12.3)*].

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

The recommended dose of Tasigna (nilotinib) is 400 mg orally twice daily [see *Clinical Pharmacology (12.3)*].

2.2 Dose Adjustments or Modifications

QT interval prolongation:

Table 1: Dose Adjustments for QT Prolongation

ECGs with a QTc >480 msec	<ol style="list-style-type: none"> 1. Withhold Tasigna, 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 <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 >480 msec, Tasigna should be discontinued. 5. An ECG should be repeated approximately 7 days after any dose adjustment.
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Myelosuppression

Tasigna may need to be withheld and/or dose reduced 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	ANC* <1.0 x 10 ⁹ /L and/or platelet counts <50 x 10 ⁹ /L	<ol style="list-style-type: none"> 1. Stop Tasigna, and monitor blood counts 2. Resume within 2 weeks at prior dose if ANC >1.0 x 10⁹/L and platelets >50 x 10⁹/L 3. If blood counts remain low for >2 weeks, reduce the dose to 400 mg once daily
Resistant or intolerant Ph+ CML in chronic phase or accelerated phase at 400 mg twice daily		

*ANC = absolute neutrophil count

See Table 3 for dose adjustments for elevations of lipase, amylase, bilirubin, and/or hepatic transaminases [*see Adverse Reactions (6.1)*].

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

Elevated serum lipase or amylase ≥Grade 3	<ol style="list-style-type: none"> 1. Withhold Tasigna, and monitor serum lipase or amylase 2. Resume treatment at 400 mg once daily if serum lipase or amylase returns to ≤Grade 1
Elevated bilirubin ≥Grade 3	<ol style="list-style-type: none"> 1. Withhold Tasigna, and monitor bilirubin 2. Resume treatment at 400 mg once daily if bilirubin returns to ≤Grade 1
Elevated hepatic transaminases ≥Grade 3	<ol style="list-style-type: none"> 1. Withhold Tasigna, and monitor hepatic transaminases 2. Resume treatment at 400 mg once daily if hepatic transaminases returns 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 CML-AP) 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 [see *Warnings and Precautions* (5.4, 5.5), *Use in Specific Populations* (8.7)].

Hepatic Impairment

If possible, consider alternative therapies. If Tasigna 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) [see *Warnings and Precautions* (5.9), *Use in Specific Populations* (8.7)].

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). Grapefruit products may also increase serum concentrations of nilotinib and should be avoided. Should treatment with any of these agents be required, it is recommended that therapy with Tasigna 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 Tasigna dose is adjusted upward to the indicated dose. Close monitoring for prolongation of the QT interval is indicated for patients who cannot avoid strong CYP3A4 inhibitors [see *Boxed Warning*, *Warnings and Precautions* (5.2, 5.7), *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). Patients should also refrain from taking St. John's Wort. Based on the nonlinear pharmacokinetic profile of nilotinib, increasing the dose of Tasigna when co-administered with such agents is unlikely to compensate for the loss of exposure [see *Drug Interactions* (7.2)].

3 DOSAGE FORMS AND STRENGTHS

150 mg red opaque hard gelatin capsules with black axial imprint “NVR/BCR”.

200 mg light yellow opaque hard gelatin capsules with a red axial imprint “NVR/TKI”.

4 CONTRAINDICATIONS

Do not use in patients with hypokalemia, hypomagnesemia, or long QT syndrome [*see Boxed Warning*].

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

Treatment with Tasigna can cause Grade 3/4 thrombocytopenia, neutropenia and anemia. Perform complete blood counts every two weeks for the first 2 months and then monthly thereafter, or as clinically indicated. Myelosuppression was generally reversible and usually managed by withholding Tasigna temporarily or dose reduction [*see Dosage and Administration (2.2)*].

5.2 QT Prolongation

Tasigna 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 (12.4)*]. 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, seven days after initiation, periodically as clinically indicated and following dose adjustments [*see Warnings and Precautions (5.13)*].

Tasigna should not be used in patients who have hypokalemia, hypomagnesemia or long QT syndrome. Hypokalemia or hypomagnesemia must be corrected prior to initiating Tasigna and these electrolytes should be monitored periodically during therapy [*see Warnings and Precautions (5.13)*].

Significant prolongation of the QT interval may occur when Tasigna 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 [*see Warnings and Precautions (5.7, 5.8)*]. The presence of hypokalemia and hypomagnesemia may further enhance this effect [*see Warnings and Precautions (5.6, 5.13)*].

5.3 Sudden Deaths

Sudden deaths have been reported in patients with CML treated with nilotinib in clinical studies (n= 5,661; 0.3%). 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 Elevated Serum Lipase

The use of Tasigna can cause increases in serum lipase. Caution is recommended in patients with a previous history of pancreatitis. 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.

5.5 Hepatotoxicity

The use of Tasigna may result in elevations in bilirubin, AST/ALT, and alkaline phosphatase. Hepatic function tests should be checked monthly or as clinically indicated [*see Warnings and Precautions (5.13)*].

5.6 Electrolyte Abnormalities

The use of Tasigna can cause hypophosphatemia, hypokalemia, hyperkalemia, hypocalcemia, and hyponatremia. Electrolyte abnormalities must be corrected prior to initiating Tasigna and these electrolytes should be monitored periodically during therapy [*see Warnings and Precautions (5.13)*].

5.7 Drug Interactions

The administration of Tasigna with agents that are 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 be avoided. Should treatment with any of these agents be required, it is recommended that therapy with Tasigna be interrupted. If interruption of treatment with Tasigna 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)*].

5.8 Food Effects

The bioavailability of nilotinib is increased with food. Tasigna must not be taken with food. No food should be taken at least 2 hours before and at least one hour after the dose is taken. Grapefruit products and other foods that are known to inhibit CYP3A4 should be avoided [*see Boxed Warning, Drug Interactions (7.2) and Clinical Pharmacology (12.3)*].

5.9 Hepatic Impairment

Nilotinib exposure is increased in patients with impaired hepatic function. A lower starting dose is recommended for patients with mild to severe hepatic impairment (at baseline) and QT interval should be monitored closely [*see Dosage and Administration (2.2) and Use in Specific Populations (8.7)*].

5.10 Tumor Lysis Syndrome

Cases of tumor lysis syndrome have been reported in Tasigna 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 Tasigna.

5.11 Total Gastrectomy

The exposure of nilotinib is reduced in patients with total gastrectomy. More frequent follow-up of these patients should be considered. Dose increase or alternative therapy may be considered in patients with total gastrectomy [*see Clinical Pharmacology 12.3*].

5.12 Lactose

Since the capsules contain lactose, Tasigna 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.

5.13 Monitoring Laboratory Tests

Complete blood counts should be performed every two weeks for the first two months and then monthly thereafter. Chemistry panels, including the lipid profile, should be checked periodically. ECGs should be obtained at baseline, seven days after initiation and periodically thereafter, as well as following dose adjustments [*see Warnings and Precautions (5.2)*]. Laboratory monitoring for patients receiving Tasigna may need to be performed more or less frequently at the physician's discretion.

5.14 Use in Pregnancy

There are no adequate and well controlled studies of Tasigna in pregnant women. However, Tasigna 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 Tasigna [*see Use in Specific Populations (8.1)*].

6 ADVERSE REACTIONS

The following serious adverse reactions can occur with Tasigna 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)*]

Elevated serum lipase [*see Warnings and Precautions (5.4)*]

Hepatotoxicity [*see Warnings and Precautions (5.5)*]

Electrolyte abnormalities [*see Boxed Warning, Warnings and Precautions (5.6)*]

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.

Newly diagnosed Ph+ CML-CP

The data below reflect exposure to Tasigna from a randomized trial in newly diagnosed patients with 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 25 months (range 0.1 – 35.4 months). The median actual dose intensity was 594 mg/day in the nilotinib 300 mg twice daily group.

The most common (>10%) non-hematologic adverse drug reactions were rash, pruritus, headache, nausea, fatigue and myalgia. Upper abdominal pain, alopecia, constipation, diarrhea, dry skin, muscle spasms, arthralgia, abdominal pain, peripheral edema, vomiting and asthenia were observed less commonly (≤10% and >5%) and have been of mild to moderate severity, manageable and generally did not require dose reduction. Pleural and pericardial effusions occurred in 1% of patients. Gastrointestinal hemorrhage was reported in 2.5% of patients.

Increase in QTcF >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 >500 msec while on study drug.

The most common hematologic adverse drug reactions (all grades) were myelosuppression including: thrombocytopenia (17%), neutropenia (15%) and anemia (7%). See Table 7 for Grade 3/4 laboratory abnormalities.

Discontinuation due to adverse events regardless of causality was observed in 9% of patients.

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; CML-AP=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 1-1096) and 264 (range 2-1160), respectively. The median dose intensity for patients with CML-CP and CML-AP is 789 mg/day (range 151–1110) and 780 mg/day (range 150-1149), 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 1-345), and the median duration in days of dose interruptions for the CML-AP patients was 23 (range 1–234).

In patients with CML-CP, the most commonly reported non-hematologic adverse drug reactions ($\geq 10\%$) were rash, pruritus, nausea, fatigue, headache, constipation, diarrhea, vomiting and myalgia. The common serious drug-related adverse reactions ($\geq 1\%$ and $< 10\%$) were thrombocytopenia, neutropenia and anemia.

In patients with CML-AP, the most commonly reported non-hematologic adverse drug reactions ($\geq 10\%$) were rash, pruritus and fatigue. The common serious adverse drug reactions ($\geq 1\%$ and $< 10\%$) 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 > 60 msec from baseline was observed in 4.1% of the patients and QTcF of > 500 msec was observed in 4 patients ($< 1\%$) [see *Boxed Warning, Warnings and Precautions (5.2, 5.3), Clinical Pharmacology (12.4)*].

Discontinuation due to drug-related adverse 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 drug reactions (excluding laboratory abnormalities) regardless of relationship to study drug. Adverse reactions reported in greater than 10% of patients who received at least one dose of Tasigna are listed.

Table 5: Most Frequently Reported Non-hematologic Adverse Reactions (Regardless of Relationship to Study Drug) in Patients with Newly Diagnosed Ph+ CML-CP (≥10% in Tasigna 300 mg twice daily or Imatinib 400 mg once daily groups)^a

Patients with Newly Diagnosed Ph+ CML-CP						
		TASIGNA 300 mg twice daily N=279	Imatinib 400 mg once daily N=280	TASIGNA 300 mg twice daily N=279	Imatinib 400 mg once daily N=280	
		All Grades (%)			CTC Grades ^b 3 / 4 (%)	
	Body System and Preferred Term					
		Skin and subcutaneous tissue disorders	Rash	37	18	<1
		Pruritus	20	7	<1	0
		Alopecia	11	6	0	0
		Periorbital edema	<1	15	0	0
	Gastrointestinal disorders	Nausea	20	39	1	1
		Constipation	17	6	0	0
		Diarrhea	14	40	<1	2
		Vomiting	11	24	0	<1
		Abdominal pain upper	15	11	<1	<1
		Abdominal pain	14	10	1	0
	Nervous system disorders	Headache	30	18	3	<1
	General disorders and administration site conditions	Fatigue	21	16	1	1
		Pyrexia	11	12	<1	0
		Asthenia	11	10	<1	0
		Edema, peripheral	8	18	0	0
		Face edema	<1	11	0	<1
	Musculoskeletal and connective tissue disorders	Myalgia	14	18	<1	0
		Arthralgia	17	13	<1	<1
Muscle spasms		11	31	0	<1	
Pain in extremity		11	13	<1	<1	
	Back pain	14	11	<1	1	
Respiratory, thoracic and mediastinal disorders	Cough	14	9	0	0	
Infections and infestations	Nasopharyngitis	22	17	0	0	
	Upper respiratory tract infection	14	10	<1	0	
Eye disorders	Eyelid edema	1	16	0	<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 Tasigna 400 mg Twice Daily (Regardless of Relationship to Study Drug) (≥10% in any Group)^a

Body System and Preferred Term		CML-CP			CML-AP		
		N=321		CTC Grades ^b 3 / 4 (%)	N=137		CTC Grades ^b 3 / 4 (%)
		All Grades (%)			All Grades (%)		
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
	Headache	35	2		20		1
Nervous system disorders	Fatigue	32	3		23		<1
	Pyrexia	22	<1		28		2
	Asthenia	16	0		14		1
	Edema, peripheral	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
Respiratory, thoracic and mediastinal disorders	Pain in extremity	20	2		18		1
	Back pain	17	2		15		<1
	Musculoskeletal pain	11	<1		12		1
	Cough	27	<1		18		0
Infections and infestations	Dyspnea	15	2		9		2
	Oropharyngeal pain	11	0		7		0
	Nasopharyngitis	24	<1		15		0
	Upper respiratory tract infection	12	0		10		0
Metabolism and nutrition disorders	Anorexia	12	<1		15		<1
	Insomnia	12	1		7		0
	Hypertension	10	2		11		<1
	Psychiatric disorders						
Vascular disorders							

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

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 Tasigna.

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

	Patient Population			
	Newly Diagnosed Ph+ CML-CP		Resistant or Intolerant Ph+	
			CML-CP	CML-AP
	TASIGNA 300 mg twice daily N=279 (%)	Imatinib 400 mg once daily N=280 (%)	TASIGNA 400 mg twice daily N=321 (%)	TASIGNA 400 mg twice daily N=137 (%)
Hematologic Parameters				
Thrombocytopenia	10	9	30 ¹	42 ³
Neutropenia	12	21	31 ²	42 ⁴
Anemia	4	5	11	27
Biochemistry Parameters				
Elevated lipase	7	3	18	18
Hyperglycemia	6	0	12	6
Hypophosphatemia	5	8	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	0	4	3
Hypocalcemia	<1	0	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

¹CML-CP: Thrombocytopenia: 12% were grade 3, 18% were grade 4

²CML-CP: Neutropenia: 16% were grade 3, 15% were grade 4

³CML-AP: Thrombocytopenia: 11% were grade 3, 32% were grade 4

⁴CML-AP: Neutropenia: 16% were grade 3, 26% were grade 4

6.2 Additional Data from Clinical Trials

The following adverse drug reactions were reported in patients in the Tasigna 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 ($\geq 1\%$ and $< 10\%$), uncommon ($\geq 0.1\%$ and $< 1\%$), and unknown frequency (single events). For adverse drug reactions listed under “Investigations”, very common events ($\geq 10\%$), 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.

Infections and Infestations: Common: folliculitis. Uncommon: upper respiratory tract infection (including nasopharyngitis, pharyngitis, rhinitis), pneumonia, bronchitis, urinary tract infection, candidiasis (including oral

candidiasis), gastroenteritis. Unknown frequency: sepsis, subcutaneous abscess, anal abscess, furuncle, tinea pedis.

Neoplasms Benign, Malignant and Unspecified: Common: Skin papilloma. Unknown frequency: oral papilloma.

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

Immune System Disorders: Unknown frequency: hypersensitivity.

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

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

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

Nervous System Disorders: Common: dizziness, peripheral neuropathy, hypoesthesia, paresthesia. Uncommon: intracranial hemorrhage, migraine, loss of consciousness (including syncope), tremor, disturbance in attention, hyperesthesia. Unknown frequency: brain edema, optic neuritis, lethargy, dysesthesia, restless legs syndrome.

Eye Disorders: Common: eye hemorrhage, periorbital edema, eye pruritus, conjunctivitis, dry eye. Uncommon: vision impairment, vision blurred, visual acuity reduced, photopsia, hyperemia (scleral, conjunctival, ocular), eye irritation. Unknown frequency: papilloedema, diplopia, photophobia, eye swelling, blepharitis, eye pain, chorioretinopathy, conjunctival hemorrhage, 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, pericardial effusion, coronary artery disease, cyanosis, cardiac murmur. Unknown frequency: myocardial infarction, ventricular dysfunction, pericarditis, ejection fraction decrease.

Vascular Disorders: Common: hypertension, flushing. Uncommon: hypertensive crisis, peripheral arterial occlusive disease, hematoma. Unknown frequency: shock hemorrhagic, hypotension, thrombosis.

Respiratory, Thoracic and Mediastinal Disorders: Common: dyspnea, dyspnea exertional, epistaxis, cough, 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, dyspepsia, dysgeusia, flatulence. Uncommon: gastrointestinal hemorrhage, melena, mouth ulceration, gastroesophageal reflux, stomatitis, esophageal pain, dry mouth. Unknown frequency: gastrointestinal ulcer perforation, retroperitoneal hemorrhage, hematemesis, gastric ulcer, esophagitis ulcerative, subileus, gastritis, enterocolitis, hemorrhoids, hiatus hernia, rectal hemorrhage, gingivitis.

Hepatobiliary Disorders: Common: hepatic function abnormal. Uncommon: hepatotoxicity, hepatitis, jaundice. Unknown frequency: cholestasis, hepatomegaly.

Skin and Subcutaneous Tissue Disorders: Common: night sweats, eczema, urticaria, erythema, hyperhidrosis, contusion, acne, dermatitis (including allergic and acneiform), dry skin. Uncommon: exfoliative rash, drug eruption, pain of skin, ecchymosis, swelling of face. Unknown frequency: 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.

Musculoskeletal and Connective Tissue Disorders: Common: bone pain, musculoskeletal chest pain, musculoskeletal pain, flank pain. Uncommon: musculoskeletal stiffness, muscular weakness, 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 (including neck pain and back pain), chest discomfort, malaise. Uncommon: face edema, gravitational edema, influenza-like illness, chills, feeling body temperature change (including feeling hot, feeling cold). Unknown frequency: localized edema.

Investigations: Common: hemoglobin decreased, blood amylase increased, gamma-glutamyltransferase increased, blood creatinine phosphokinase increased, blood alkaline phosphatase increased, weight decreased, weight increased. Uncommon: blood lactate dehydrogenase increased, blood urea increased. Unknown frequency: troponin increased, blood bilirubin unconjugated increased, blood insulin increased, lipoprotein increased (including very low density and high density), 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.

Single-dose administration of Tasigna with midazolam (a CYP3A4 substrate) to healthy subjects increased midazolam exposure by 30%. Single-dose administration of Tasigna to healthy subjects did not change the pharmacokinetics and pharmacodynamics of warfarin (a CYP2C9 substrate). The ability of Tasigna to induce metabolism has not been determined *in vivo*. Exercise caution when co-administering Tasigna with substrates for these enzymes that have a narrow therapeutic index.

Nilotinib inhibits human P-glycoprotein (P-gp). If Tasigna is administered with drugs that are substrates of P-gp, 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 Tasigna with agents that are strong CYP3A4 inhibitors should be avoided [see *Boxed Warning, Dosage and Administration (2.2), Warnings and Precautions (5.2, 5.7)*]. Concomitant use of Tasigna 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 Tasigna, 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, co-administration of a single 400 mg dose of Tasigna with multiple doses of esomeprazole (a proton pump inhibitor) at 40 mg daily decreased the nilotinib AUC by 34%. Increasing the dose of Tasigna 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. The concomitant use of proton pump inhibitors with Tasigna should be used with caution. If an H₂ blocker or an antacid is necessary, the doses between the H₂ blocker and Tasigna or the doses between the antacid and Tasigna should be separated by at least several hours. However, no clinical study has been conducted to evaluate the effect of H₂ blockers or antacids on nilotinib pharmacokinetics.

7.4 Drugs that Inhibit Drug Transport Systems

Nilotinib is a substrate of the efflux transporter P-glycoprotein (P-gp, ABCB1). If Tasigna 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 Tasigna with agents that may prolong the QT interval such as anti-arrhythmic medicines should be avoided [*see Boxed Warning, Dosage and Administration (2.2), Warnings and Precautions (5.2, 5.7)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D [*see Warnings and Precautions (5.14)*].

Based on its mechanism of action and findings in animals, Tasigna may cause fetal harm when administered to a pregnant woman. There are no adequate and well controlled studies with Tasigna in pregnant women. Women should be advised to avoid becoming pregnant while on Tasigna. 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.

Nilotinib was studied for effects on embryo-fetal development in pregnant rats and rabbits given oral doses of 10, 30, 100 mg/kg/day, and 30, 100, 300 mg/kg/day, respectively, during organogenesis. In rats, nilotinib at doses of 100 mg/kg/day (approximately 5.7 times the AUC in patients at the dose of 400 mg twice daily) was associated with maternal toxicity (decreased gestation weight, gravid uterine weight, net weight gain, and food consumption). Nilotinib at doses ≥ 30 mg/kg/day (approximately 2 times the AUC in patients at the dose of 400 mg twice daily) resulted in embryo-fetal toxicity as shown by increased resorption and post-implantation loss, and at 100 mg/kg/day, a decrease in viable fetuses. In rabbits, maternal toxicity at 300 mg/kg/day (approximately one-half the human exposure based on AUC) was associated with mortality, abortion, decreased gestation weights and decreased food consumption. Embryonic toxicity (increased resorption) and minor skeletal anomalies were observed at a dose of 300 mg/kg/day. Nilotinib is not considered teratogenic.

When pregnant rats were dosed with nilotinib during organogenesis and through lactation, the adverse effects included a longer gestational period, lower pup body weights until weaning and decreased fertility indices in the pups when they reached maturity, all at a maternal dose of 360 mg/m² (approximately 0.7 times the clinical dose of 400 mg twice daily based on body surface area). At doses up to 120 mg/m² (approximately 0.25 times the clinical dose of 400 mg twice daily based on body surface area) no adverse effects were seen in the maternal animals or the pups.

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 Tasigna, 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 Tasigna in pediatric patients have not been established.

8.5 Geriatric Use

In the clinical trials of Tasigna (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 <65 years and those ≥65 years.
- Patients with resistant or intolerant CML-CP: There was no difference in major cytogenetic response rate between patients aged <65 years and those ≥65 years.
- Patients with resistant or intolerant CML-AP: The hematologic response rate was 44% in patients <65 years of age and 29% in patients ≥65 years.

No major differences for safety were observed in patients ≥65 years of age as compared to patients <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 Tasigna, the mean AUC values were increased on average of 35%, 35% and 56% in subjects with mild (Child-Pugh class A, score 5-6), moderate (Child-Pugh class B, score 7-9) and severe hepatic impairment (Child-Pugh class C, score 10-15), 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 (5.9)*].

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

8.8 Renal Impairment

Clinical studies have not been performed in patients with impaired renal function. Clinical studies have excluded patients with serum creatinine concentration >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.

10 OVERDOSAGE

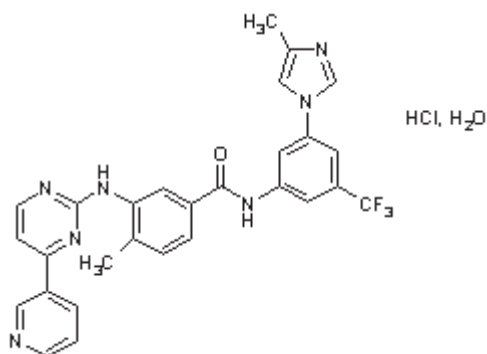
Overdose with nilotinib has been reported, where an unspecified number of Tasigna capsules were ingested in combination with alcohol and other drugs. Events included neutropenia, vomiting, and drowsiness. In the event of overdose, the patient should be observed and appropriate supportive treatment given.

11 DESCRIPTION

Tasigna (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 $C_{28}H_{22}F_3N_7O \cdot HCl \cdot H_2O$ and 584. The solubility of nilotinib in aqueous solutions decreases with increasing pH. Nilotinib is not optically active. The pK_{a1} was determined to be 2.1; pK_{a2} 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:



Tasigna (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 polyoxamer 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 (20-60 nM), PDGFR (69 nM), c-KIT (210 nM), CSF-1R (125-250 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 one 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* (5.11)].

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.

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%-50% for nilotinib and approximately 20% for imatinib.

12.4 QT/QTc Prolongation

In a placebo-controlled study in healthy volunteers designed to assess the effects of Tasigna on the QT interval, administration of Tasigna 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)*].

12.5 Pharmacogenomics

Tasigna can increase bilirubin levels. A pharmacogenetic analysis of 97 patients evaluated the polymorphisms of UGT1A1 and its potential association with hyperbilirubinemia during Tasigna 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 (5.5)*].

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 2-3 fold the human exposure (based on AUC) at the nilotinib dose of 400 mg twice daily. The study was negative for carcinogenic findings.

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 4-7 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 Tasigna on human fertility is unknown. In a study where male and female rats were treated with nilotinib at oral doses of 20-180 mg/kg/day (approximately 1-6.6 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 Tasigna versus imatinib tablets in adult patients with cytogenetically confirmed newly diagnosed Ph+ CML-CP. Patients were within six 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 ≥ 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). A second data analysis was performed when all 846 patients completed 24 months of

treatment (or discontinued earlier). The median time on treatment at the time of the second analysis was 25 months in all three treatment groups. This study is on-going and further data will be required to determine long-term outcome.

The primary efficacy endpoint was major molecular response (MMR) at 12 months after the start of study medication. MMR was defined as $\leq 0.1\%$ BCR-ABL/ABL % by international scale measured by RQ-PCR, which corresponds to a ≥ 3 log reduction of BCR-ABL transcript from standardized baseline. Efficacy endpoints are summarized in Table 9 below. After 24 months of minimum follow-up, two patients on the nilotinib arm progressed to either accelerated phase or blast crisis while 17 patients on the imatinib arm progressed to either accelerated phase or blast crisis.

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

	TASIGNA 300 mg twice daily	Imatinib 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 ≥ 20 metaphase cells in each bone marrow sample.

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 Tasigna (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/day for patients with CML-CP and CML-AP, and the highest prior imatinib dose was ≥ 600 mg/day in 74% of all patients with 40% of patients receiving imatinib doses ≥ 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 CML-AP patients are reported in Table 10.

Median durations of response had not been reached at the time of data analysis.

Table 10: Efficacy of Tasigna 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%-35%). Cytogenetic responses were based on the percentage of Ph-positive metaphases among ≥ 20 metaphase cells in each bone marrow sample.

^b Hematologic response = CHR + NEL (all responses confirmed after 4 weeks).

CHR (CML-CP): WBC $< 10 \times 10^9/L$, platelets $< 450,000/mm^3$, no blasts or promyelocytes in peripheral blood, $< 5\%$ myelocytes + metamyelocytes in bone marrow, $< 20\%$ basophils in peripheral blood, and no extramedullary involvement.

CHR (CML-AP): neutrophils $\geq 1.5 \times 10^9/L$, platelets $\geq 100 \times 10^9/L$, no myeloblasts in peripheral blood, myeloblasts $< 5\%$ in bone marrow, and no extramedullary involvement.

NEL: same criteria as for CHR but neutrophils $\geq 1.0 \times 10^9/L$ and platelets $\geq 20 \times 10^9/L$ 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 1.0 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

Tasigna (nilotinib) 150 mg capsules are red opaque hard gelatin capsules, size 1 with black axial imprint “NVR/BCR”. Tasigna (nilotinib) 200 mg capsules are light yellow opaque hard gelatin capsules, size 0 with the red axial imprint “NVR/TKI.” Tasigna capsules are supplied in blister packs.

150 mg

Carton of 4 blister packs of (4x28)NDC 0078-0592-87

Blisters of 28 capsules.....NDC 0078-0592-51

200 mg

Carton of 4 blister packs of (4x28)NDC 0078-0526-87

Blisters of 28 capsules.....NDC 0078-0526-51

Each blister pack contains one folded blister card of 28 capsules each, for dosing two in the morning and two in the evening at 12 hour intervals over a 7 day period.

Tasigna (nilotinib) capsules should be stored at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See Medication Guide

A Medication Guide is required for distribution with Tasigna. Encourage patients to read the Tasigna Medication Guide. The complete text of the Medication Guide is reprinted at the end of this document.

17.1 Taking Tasigna

Tasigna doses should be taken twice daily approximately 12 hours apart and should not be taken with food. The capsules should be swallowed whole with water.

Patients should be advised to take Tasigna on an empty stomach. Tasigna should be taken at least 2 hours after a meal. No food should be consumed for at least one hour after the dose is taken. Patients should not consume grapefruit products and other foods that are known to inhibit CYP3A4 at anytime during Tasigna treatment [*see Dosage and Administration (2.1), Warnings and Precautions (5.7, 5.8) and Medication Guide*].

If a dose is missed, the patient should not take a make-up dose, but should resume taking the next prescribed daily dose.

Should patients be unable to swallow capsules, the contents of each capsule may be dispersed in one teaspoon of applesauce and the mixture swallowed immediately (within 15 minutes).

17.2 Drug Interactions

Tasigna and certain other medicines, including over the counter medications or herbal supplements (such as St. John's Wort), can interact with each other [*see Warnings and Precautions (5.7) and Drug Interactions (7)*].

17.3 Pregnancy

Patients should be advised that the use of Tasigna during pregnancy may cause harm to the fetus and should not be taken during pregnancy unless necessary. Women of childbearing potential should use highly effective contraceptives if taking Tasigna. Sexually active female patients taking Tasigna should use adequate contraception [*see Warnings and Precautions (5.14) and Use in Specific Populations (8.1)*].

17.4 Compliance

Patients should be advised of the following:

- Continue taking Tasigna every day for as long as their doctor tells them.
- This is a long-term treatment.
- Do not change dose or stop taking Tasigna without first consulting their doctor.
- If a dose is missed, take the next dose as scheduled. Do not take a double dose to make up for the forgotten capsules.