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 (5.2). Sudden deaths have been reported in patients receiving nilotinib (5.3). Tasigna should not be used in patients with hypokalemia, hypomagnesemia, or long QT syndrome (4). Hypokalemia or hypomagnesemia must be corrected prior to Tasigna administration and should be periodically monitored (5.2). Drugs known to prolong the QT interval and strong CYP3A4 inhibitors should be avoided (5.7). Patients should avoid food 2 hours before and 1 hour after taking dose (5.8). Use with caution in patients with hepatic impairment (5.9). ECGs should be obtained to monitor the QTc at baseline, seven days after initiation, and periodically thereafter, as well as following any dose adjustments. (5.2, 5.3, 5.6, 5.12)

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

Tasigna is a kinase inhibitor indicated for the treatment of chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukemia (CML) in adult patients resistant to or intolerant to prior therapy that included imatinib.(1)

----------DOSAGE AND ADMINISTRATION----------

- 400 mg orally twice daily, approximately 12 hours apart and should not be taken with food. (2)
- 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. (2)
- Dose adjustment may be required for hematologic and non-hematologic toxicities, and drug interactions. (2)

----------DOSAGE FORMS AND STRENGTHS----------

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 caution in patients with hepatic impairment. Obtain ECGs at baseline, seven days after initiation, and periodically thereafter, as well as following any dose adjustments. (5.2, 5.3, 5.6, 5.12)
- Sudden deaths: There were sudden deaths reported in the safety population and the expanded access program. Ventricular repolarization abnormalities may have contributed to their occurrence. (5.3)
- Elevated serum lipase: Caution is recommended in patients with history of pancreatitis. Check serum lipase periodically. (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, 5.12)
- Hepatic impairment: Tasigna has not been investigated in patients with hepatic impairment. Caution is recommended in these patients and QT interval should be monitored closely. (5.9)
  - 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)
  - Pregnancy: Fetal harm can occur when administered to a pregnant woman. Women should be advised not to become pregnant when taking Tasigna. (5.11, 8.1)

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

In CML-CP patients, the most commonly reported drug-related adverse reactions (>10%) were rash, pruritis, nausea, fatigue, headache, constipation, diarrhea and vomiting. The common serious drug-related adverse reactions were thrombocytopenia and neutropenia. In CML-AP patients, the most commonly reported drug-related adverse reactions (>10%) were rash, pruritus and constipation. The common serious drug-related adverse reactions were thrombocytopenia, neutropenia, pneumonia, febrile neutropenia, leukopenia, intracranial hemorrhage, elevated lipase and pyrexia. (6.1)

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

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

CYP3A4 inhibitors may affect serum concentration (7.1)

CYP3A4 inducers may affect serum concentration (7.2)

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 (7.3)

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

- Should not be used during pregnancy (8.1)
- 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)
- Use with caution in patients with hepatic impairment (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: October/2007

FULL PRESCRIBING INFORMATION: CONTENTS *

* Sections or subsections omitted from Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: QT PROLONGATION AND SUDDEN DEATHS

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1 INDICATIONS AND USAGE

Tasigna (nilotinib) is indicated for the treatment of chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukemia (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*)]. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The recommended dose of Tasigna (nilotinib) is 400 mg orally twice daily. *[See Clinical Pharmacology (12.3)]*. Treatment should continue as long as the patient does not show evidence of progression or unacceptable toxicity.

Tasigna should be taken twice daily at approximately 12 hour intervals and should 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) and Clinical Studies (14)*.

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

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.

2.2 Dose Adjustments or Modifications

QT interval prolongation:

Table 1 Dose Adjustments for QT prolongation

ECGs with a QTc > 480 msec	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 <450msec 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.

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

Chronic Phase or Accelerated Phase CML at 400 mg twice daily	ANC* < 1.0 x 10^9/L and/or platelet counts < 50 x 10^9/L	1. Stop Tasigna, and monitor blood counts 2. Resume within 2 weeks at prior dose if ANC >1.0 x 10^9/L and platelets >50 x 10^9/L 3. If blood counts remain low for > 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. *[See Adverse Reactions (6.1)]*

Table 3 Dose Adjustments for selected non-hematologic laboratory abnormalities

Elevated serum lipase or amylase ≥ Grade 3	1. Withhold Tasigna, and monitor serum lipase or amylase 2. Resume treatment at 400 mg once daily if serum lipase or amylase return to ≤ Grade 1
Elevated bilirubin ≥ Grade 3	1. Withhold Tasigna, and monitor bilirubin 2. Resume treatment at 400 mg once daily if bilirubin return to ≤ Grade 1
Elevated hepatic transaminases ≥ Grade 3	1. Withhold Tasigna, and monitor hepatic transaminases 2. Resume treatment at 400 mg once daily if hepatic transaminases return to ≤ Grade 1

Other non-hematologic toxicities: If other clinically significant moderate or severe non-hematologic toxicity develops, dosing should be withheld, and may be resumed at 400 mg once daily when the toxicity has resolved. If clinically appropriate, escalation of the dose back to 400 mg twice daily should be considered. *[See Warnings and Precautions (5) and Use in Specific Populations (8)]*.

Concomitant Strong CYP3A4 Inhibitors: The concomitant use of strong CYP3A4 inhibitors should be avoided (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, 400 mg once daily (a dose reduction to 1/2 of the original daily dose) is predicted to adjust the nilotinib AUC to the AUC observed without inhibitors. 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 and 5.7) and Drug Interactions (7.2)]*.

Concomitant Strong CYP3A4 Inducers: The concomitant use of strong CYP3A4 inducers should be avoided (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital).

inducer, the dose of Tasigna may need to be increased, depending on patient tolerability. If the strong inducer is discontinued the nilotinib dose should be reduced to the indicated dose. *[See Drug Interactions (7.2)]*

3 DOSAGE FORMS AND STRENGTHS

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 (nilotinib) can cause Grade 3/4 thrombocytopenia, neutropenia and anemia. Complete blood counts should be performed 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)]*

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. 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.

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. Avoid drugs known to prolong the QT interval and strong CYP3A4 inhibitors. ECGs should be performed at baseline, seven days after initiation, periodically as clinically indicated and following dose adjustments. *[See Clinical Pharmacology (12.4)]*

5.3 Sudden Deaths

There were five sudden deaths reported in patients receiving nilotinib in an on-going study (n=867; 0.6%). A similar incidence was also reported in the expanded access program. 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. Serum lipase should be checked periodically.

5.5 Hepatotoxicity

The use of Tasigna may result in elevations in bilirubin, AST/ALT, and alkaline phosphatase. Hepatic function tests should be checked periodically.

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.

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