

## 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). A dose reduction is recommended 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).

#### RECENT MAJOR CHANGES

Indications and Usage: Newly diagnosed Ph+ CML-CP (1.1) 06/2010  
Dosage and Administration: Recommended Dosing (2.1), Dose Adjustments or Modifications (2.2) 06/2010  
Warnings and Precautions: Myelosuppression (5.1), Sudden Deaths (5.3), Elevated Serum Lipase (5.4), Total Gastrectomy (5.10) 06/2010

#### INDICATIONS AND USAGE

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)

Treatment of chronic phase (CP) and accelerated phase (AP) Ph+ CML in adult patients resistant to or intolerant to prior therapy that included imatinib. Clinical benefit, such as improvement in disease-related symptoms or increased survival, has not been demonstrated. (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, 5.12)

- 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. (5.3)
- 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, 5.12)
- 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)
- 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 (5.10).
- Pregnancy: Fetal harm can occur when administered to a pregnant woman. Women should be advised not to become pregnant when taking Tasigna. (5.13, 8.1)

#### ADVERSE REACTIONS

The most commonly reported non-hematologic adverse reactions ( $\geq 10\%$ ) 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 urinary 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](http://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

Revised: 06/2010

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## FULL PRESCRIBING INFORMATION

### WARNING: QT PROLONGATION AND SUDDEN DEATHS

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). A dose reduction is recommended 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)

## 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)*]. 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

#### 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)*]. 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)*].

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	<ol style="list-style-type: none"> <li>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.</li> <li>2. Resume within 2 weeks at prior dose if QTcF returns to &lt;450 msec and to within 20 msec of baseline.</li> <li>3. If QTcF is between 450 msec and 480 msec after 2 weeks reduce the dose to 400 mg once daily.</li> <li>4. If, following dose-reduction to 400 mg once daily, QTcF returns to &gt;480 msec, Tasigna should be discontinued.</li> <li>5. An ECG should be repeated approximately 7 days after any dose adjustment.</li> </ol>
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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**

<p>Newly diagnosed Ph+ CML in chronic phase at 300 mg twice daily</p> <p>Resistant or intolerant Ph+ CML in chronic phase or accelerated phase at 400 mg twice daily</p>	<p>ANC* &lt;1.0 x 10<sup>9</sup>/L and/or platelet counts &lt;50 x 10<sup>9</sup>/L</p>	<ol style="list-style-type: none"> <li>1. Stop Tasigna, and monitor blood counts</li> <li>2. Resume within 2 weeks at prior dose if ANC &gt;1.0 x 10<sup>9</sup>/L and platelets &gt;50 x 10<sup>9</sup>/L</li> <li>3. If blood counts remain low for &gt;2 weeks, reduce the dose to 400 mg once daily</li> </ol>
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\*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, 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 Boxed Warning, 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 (5.12)*].

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 (5.12)*].

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, 5.12)*].

### **5.3 Sudden Deaths**

Sudden deaths have been reported in patients with resistant or intolerant Ph+ CML receiving nilotinib (n=867; 0.6%). A similar incidence was also reported in the expanded access program for patients with resistance or intolerant Ph+ CML. 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 (5.12)*].

### **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 (5.12)*].

### **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 Boxed Warning, Dosage and Administration (2.2) and Use in Specific Populations (8.7)*].

## 5.10 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*].

## 5.11 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.

## 5.12 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.

## 5.13 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 18.6 months. The median actual dose intensity was 593 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 and asthenia were observed less commonly ( $\leq 10\%$  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 0.4% 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.

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 for adverse events regardless of causality was observed in 7% of patients.

### **Resistant or intolerant Ph+ CML-CP and CML-AP**

In the single open-label multicenter clinical trial, a total of 438 patients with Ph+ CML-CP and CML-AP resistant to or intolerant to at least one prior therapy including imatinib were treated (CML-CP=318; CML-AP=120) at the recommended dose of 400 mg twice daily.

The median duration of exposure in days for CML-CP and CML-AP patients is 245 (range 1-502) and 138 (range 2-503), respectively. The median dose intensity of 797 mg/day (range 145–1149) was similar for both the chronic and accelerated phase patients 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 18 (range 1-185), and the median duration in days of dose interruptions for the CML-AP patients was 22 (range 1–163).

In CML-CP patients, the most commonly reported adverse drug reactions (>10%) were rash, pruritus, 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 adverse drug reactions (>10%) were rash, pruritus and constipation. The common serious adverse drug reactions were thrombocytopenia, neutropenia, pneumonia, febrile neutropenia, 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 2.1% of the patients and QTcF of  $>500$  msec was observed in 3 patients ( $<1\%$ ) [*see Boxed Warning, Warnings and Precautions (5.2, 5.3), Clinical Pharmacology (12.4)*].

Discontinuation for drug-related adverse reactions was observed in 11% of CML-CP and 8% of CML-AP patients.

### **Most Frequently Reported Adverse Reactions**

Tables 5 and 6 show the percentage of patients experiencing treatment-emergent adverse 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 Tasisna 300 mg twice daily or Gleevec 400 mg once daily groups)<sup>a</sup>**

		Patients with Newly Diagnosed Ph+ CML-CP				
		TASIGNA 300 mg twice daily	GLEEVEC 400 mg once daily	TASIGNA 300 mg twice daily	GLEEVEC 400 mg once daily	
		N=279	N=280	N=279	N=280	
<b>Body System and Preferred Term</b>		<b>All Grades</b>		<b>CTC Grades<sup>b</sup> 3 / 4 (%)</b>		
Skin and subcutaneous tissue disorders	Rash	36	16	<1	1	
	Pruritus	19	7	<1	0	
	Alopecia	10	5	0	0	
Gastrointestinal disorders	Nausea	19	38	1	1	
	Constipation	15	4	0	0	
	Diarrhea	14	37	<1	2	
	Vomiting	9	22	0	<1	
	Abdominal pain upper	15	10	<1	<1	
	Abdominal pain	12	9	1	<1	
	Headache	28	16	3	<1	
Nervous system disorders	Headache	28	16	3	<1	
	General disorders and administration site conditions	Fatigue	19	14	<1	1
		Pyrexia	10	12	0	0
		Asthenia	11	9	<1	0
Edema, peripheral		8	17	0	0	
Musculoskeletal and connective tissue disorders	Myalgia	14	16	<1	0	
	Arthralgia	15	13	<1	0	
	Muscle spasms	10	29	0	<1	
	Pain in extremity	9	13	0	<1	
	Back pain	12	10	<1	1	
Respiratory, thoracic and mediastinal disorders	Cough	12	9	0	0	
Infections and infestations	Nasopharyngitis	19	15	0	0	
	Upper respiratory tract infection	13	9	0	0	
Eye disorders	Eyelid edema	1	14	0	<1	

<sup>a</sup> Excluding laboratory abnormalities

<sup>b</sup> 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 Tassigna 400 mg twice daily (Regardless of Relationship to Study Drug) (≥10% in any Group)<sup>a</sup>**

Body System and Preferred Term		CML-CP		CML-AP	
		N=318	N=318	N=120	N=120
		All Grades (%)	CTC Grades <sup>b</sup> 3 / 4 (%)	All Grades (%)	CTC Grades <sup>b</sup> 3 / 4 (%)
Skin and subcutaneous tissue disorders	Rash	33	2	28	0
	Pruritus	29	<1	20	0
Gastrointestinal disorders	Nausea	31	1	18	<1
	Constipation	21	<1	18	0
	Diarrhea	22	3	19	2
	Vomiting	21	<1	10	0
	Abdominal pain	11	1	13	3
Nervous system disorders	Headache	31	3	21	2
General disorders and administration site conditions	Fatigue	28	1	16	<1
	Pyrexia	14	1	24	2
	Asthenia	14	0	12	2
	Edema, peripheral	11	0	11	0
Musculoskeletal and connective tissue disorders	Myalgia	14	2	14	<1
	Arthralgia	18	2	16	0
	Muscle spasms	11	<1	14	0
	Bone pain	11	<1	13	<1
	Pain in extremity	13	1	16	2
	Back pain	10	<1	12	<1
Respiratory, thoracic and mediastinal disorders	Cough	17	<1	13	0
	Dyspnea	11	1	8	3
Infections and infestations	Nasopharyngitis	16	<1	11	0

<sup>a</sup> Excluding laboratory abnormalities

<sup>b</sup> 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+	
	TASIGNA 300 mg twice daily N=279 (%)	GLEEVEC 400 mg once daily N=280 (%)	CML-CP TASIGNA 400 mg twice daily N=318 (%)	CML-AP TASIGNA 400 mg twice daily N=120 (%)
<b>Hematologic Parameters</b>				
Thrombocytopenia	10	9	28 <sup>1</sup>	37 <sup>2</sup>
Neutropenia	12	20	28	37 <sup>3</sup>
Anemia	4	5	8	23
<b>Biochemistry Parameters</b>				
Elevated lipase	7	3	15	17
Hyperglycemia	6	0	11	4
Hypophosphatemia	5	8	10	10
Elevated bilirubin (total)	4	<1	9	10
Elevated SGPT (ALT)	4	3	4	2
Hyperkalemia	2	1	4	3
Hyponatremia	<1	<1	3	3
Hypokalemia	<1	1	1	5
Elevated SGOT (AST)	1	1	1	1
Decreased albumin	0	0	1	1
Hypocalcemia	<1	0	1	4
Elevated alkaline phosphatase	0	<1	1	3
Elevated creatinine	0	<1	<1	0

\*NCI Common Terminology Criteria for Adverse Events, version 3.0

<sup>1</sup>CML-CP: Thrombocytopenia: 11% were Grade 3, 17% were Grade 4

<sup>2</sup>CML-AP: Thrombocytopenia: 7% were Grade 3, 30% were Grade 4

<sup>3</sup>CML-AP: Neutropenia: 12% were Grade 3, 25% 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 (1%-10%), uncommon (0.1%-1%), and unknown frequency (single events). For adverse drug reactions listed under “Investigations”, very common events (≥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 pharyngitis, nasopharyngitis, rhinitis), pneumonia, urinary tract infection, gastroenteritis. Unknown frequency: sepsis, bronchitis, herpes virus infection, candidiasis, subcutaneous abscess, anal abscess, furuncle, tinea pedis.

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

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

*Immune System Disorders:* Unknown frequency: hypersensitivity.

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

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

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

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

*Eye Disorders:* Common: eye hemorrhage, periorbital edema, eye pruritus, conjunctivitis, dry eye. Uncommon: vision impairment, vision blurred, visual acuity reduced, photopsia, eye irritation. Unknown frequency: papilloedema, diplopia, photophobia, eye swelling, blepharitis, eye pain, chorioretinopathy, conjunctival hemorrhage, conjunctivitis allergic, conjunctival hyperaemia, ocular hyperaemia, ocular surface disease, scleral hyperaemia.

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

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

*Skin and Subcutaneous Tissue Disorders:* Common: night sweats, eczema, urticaria, erythema, hyperhidrosis, contusion, acne, dermatitis, dry skin. Uncommon: exfoliative rash, drug eruption, pain of skin, ecchymosis, swelling face. Unknown frequency: 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: pollakuria. 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, pain (including neck pain and back pain), chest discomfort. Uncommon: face edema, gravitational edema, influenza-like illness, chills, malaise. Unknown frequency: feeling hot, localized edema.

*Investigations:* Common: blood amylase increased, gamma-glutamyltransferase increased, blood creatinine phosphokinase increased, weight decreased, weight increased. Uncommon: hemoglobin decreased, blood lactate dehydrogenase increased, blood urea increased. Unknown frequency: troponin increased, blood bilirubin unconjugated increased, blood insulin increased, very low density lipoprotein increased, blood parathyroid hormone increased, blood pressure increased.

### **6.3 Postmarketing Experience**

The following additional adverse reactions have been reported during post approval use of Tasigna. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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 majority of these cases.

## **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. 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 a 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 at least by 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 (5.13)*].

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  $\geq 30$  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/m<sup>2</sup> (approximately 0.7 times the clinical dose of 400 mg twice daily based on body surface area). At doses up to 120 mg/m<sup>2</sup> (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 or over.

- Patients with newly diagnosed Ph+ CML-CP: There was no difference in major molecular response between patients aged <65 years and those  $\geq 65$  years.
- Patients with resistant or intolerant CML-CP: There was no difference in major cytogenetic response rate between patients aged <65 years and those  $\geq 65$  years.

- Patients with resistant or intolerant CML-AP: The major hematologic response rate was 31% in patients <65 years of age and 15% in patients ≥65 years.

No major differences were observed for safety 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 *Boxed Warning, 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

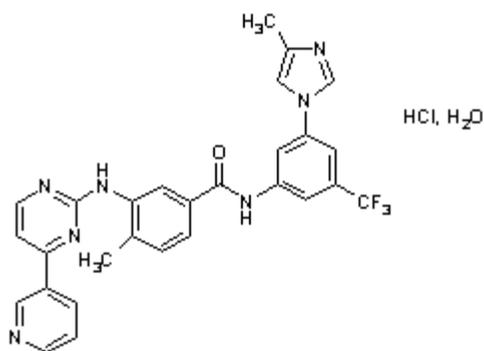
drowsiness. In the event of overdose, the patient should be observed and appropriate supportive treatment given.

## 11 DESCRIPTION

Tasigna (nilotinib) belongs to a pharmacologic class of drugs known as kinase inhibitors.

Nilotinib drug substance, a monohydrate mono-hydrochloride, 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<sup>+</sup> 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 IC<sub>50</sub> values as indicated: Bcr-Abl (20-60 nM), PDGFR (69 nM), c-Kit (210 nM), CSF-1R (125-250 nM) and DDR (3.7 nM).

### 12.3 Pharmacokinetics

#### *Absorption and Distribution:*

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 with 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.

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* (5.10)].

#### ***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)<sub>7</sub>/(TA)<sub>7</sub> genotype was associated with a statistically significant increase in the risk of hyperbilirubinemia relative to the (TA)<sub>6</sub>/(TA)<sub>6</sub> and (TA)<sub>6</sub>/(TA)<sub>7</sub> genotypes. However, the largest increases in bilirubin were observed in the (TA)<sub>7</sub>/(TA)<sub>7</sub> genotype (UGT1A1\*28) patients [see *Warnings and Precautions* (5.5)].

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with nilotinib have not been performed.

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 Gleevec<sup>®</sup> (imatinib mesylate) 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  $\geq 65$  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). The median time on treatment was 18.6 months in all three treatment groups. This study is on-going.

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  $\geq 3$  log reduction of BCR-ABL transcript from standardized baseline. Efficacy endpoints are summarized in Table 9 below.

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 of TASIGNA Compared to GLEEVEC in Newly Diagnosed Ph+ CML-CP**

	<b>TASIGNA 300 mg twice</b>	<b>GLEEVEC 400 mg once</b>
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	<b>daily</b>	<b>daily</b>
	N = 282	N = 283
MMR at 12 months (95% CI)	44% (38.4, 50.3)	22% (17.6, 27.6)
P-Value <sup>a</sup>	<0.0001	
CCyR <sup>b</sup> by 12 months (95% CI)	80% (75.0, 84.6)	65% (59.2, 70.6)

<sup>a</sup> CMH test stratified by Sokal risk group

<sup>b</sup> CCyR: 0% Ph+ metaphases. Cytogenetic responses were based on the percentage of Ph-positive metaphases among  $\geq 20$  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, 280 CML-CP patients with a minimum follow-up of 6 months and 105 CML-AP patients with a minimum follow-up of 4 months were enrolled. Of these, 232 patients with CML-CP and all patients with CML-AP were evaluable for efficacy. In this study, about 50% of CML-CP and CML-AP patients were males, over 80% 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 31 months. Prior therapy included hydroxyurea in 85% of patients, interferon in 62% and stem cell or bone marrow transplant in 8%. The median highest prior imatinib dose was 600 mg/day for CML-CP patients and 800 mg/day for CML-AP patients, and the highest prior imatinib dose was  $\geq 600$  mg/day in 77% of all patients with 44% of patients receiving imatinib doses  $\geq 800$  mg/day.

Median duration of nilotinib treatment was 8.7 months in CML-CP patients and 5.6 months in CML-AP patients.

The efficacy endpoint in chronic phase CML was unconfirmed major cytogenetic response (MCyR) which included complete and partial cytogenetic responses.

The efficacy endpoint in accelerated phase CML 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.

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

<b>Cytogenetic Response Rate (Unconfirmed) (%)<sup>a</sup></b>	<b>Chronic Phase n=232</b>
Major (95% CI)	40% (33,46)
Complete (95% CI)	28% (22,34)
Partial (95% CI)	12% (8,16)

	<b>Accelerated Phase</b> n=105
<b>Hematologic Response Rate (95% CI)<sup>b</sup></b>	26% (18,35)
Complete Hematologic Response Rate (95% CI)	18% (11,27)
No Evidence of Leukemia (95% CI)	8% (3,15)

<sup>a</sup> Cytogenetic response criteria: Complete (0% Ph+ metaphases) or partial (1%-35%). Cytogenetic responses were based on the percentage of Ph-positive metaphases among  $\geq 20$  metaphase cells in each bone marrow sample.

<sup>b</sup> Hematologic response = CHR + NEL (all responses confirmed after 4 weeks).

CHR (CML-CP): WBC  $< 10 \times 10^9$  /L, platelets  $< 450,000/\text{mm}^3$ , 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.

The median duration of response has not been reached for CML-CP and CML-AP. Based on current follow-up, 59% of CML-CP patients with a major cytogenetic response had a duration of response of at least 6 months. Based on current follow-up, 63% of CML-AP patients with a confirmed hematologic response had a duration of response of at least 6 months.

After imatinib failure, 24 different BCR-ABL mutations were noted in 19% of chronic phase and 25% of accelerated phase CML patients who were evaluated for mutations. Patients harboring a variety of BCR-ABL mutations associated with imatinib resistance, except T315I, responded to Tasigna.

## 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 all times during Tasigna treatment [*see Dosage and Administration (2.1), Warnings and Precautions (5.7, 5.8) and Medication Guide*].

### **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 effective contraceptives if taking Tasigna. Sexually active female patients taking Tasigna should use adequate contraception [*see Warnings and Precautions (5.13) 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.

## MEDICATION GUIDE

### **TASIGNA® (ta-sig-na) (nilotinib) Capsules**

Read this Medication Guide before you start taking Tasigna® and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or treatment.

#### **What is the most important information I should know about Tasigna?**

**Tasigna can cause a possible life-threatening heart problem called QTc prolongation.** QTc prolongation causes an irregular heartbeat, which may lead to sudden death.

#### **Your doctor should check the electrical activity of your heart with a test called an electrocardiogram (ECG):**

- before starting Tasigna
- 7 days after starting Tasigna
- with any dose changes
- regularly during Tasigna treatment

#### **You may lower your chances for having QTc prolongation with Tasigna if you:**

- Take Tasigna:
  - on an empty stomach. Do not take Tasigna with food.
  - at least 2 hours after eating any food, and
  - wait at least 1 hour before eating any food
- Avoid grapefruit, grapefruit juice, and any supplement containing grapefruit extract while taking Tasigna. Food and grapefruit products increase the amount of Tasigna in your body.
- Avoid taking other medicines or supplements with Tasigna that can also cause QTc prolongation.
- Tasigna can interact with many medicines and supplements and increase your chance for serious and life-threatening side effects.
- Do not take any other medicine while taking Tasigna unless your doctor tells you it is okay to do so.

**Call your doctor right away if you feel lightheaded, faint or have an irregular heartbeat while taking Tasigna.** These can be symptoms of QTc prolongation.

#### **What is Tasigna?**

Tasigna is a prescription medicine used to treat a type of leukemia called Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in adults who:

- are newly diagnosed, **or**
- are no longer benefiting from previous other treatments, including treatment with imatinib (Gleevec<sup>®</sup>), **or**
- have taken other treatments, including imatinib (Gleevec<sup>®</sup>), and cannot tolerate them

It is not known if Tasigna is safe or effective in children.

### **Who should not take Tasigna?**

Do not take if you have:

- low levels of potassium or magnesium in your blood
- long QTc syndrome

### **What should I tell my doctor before starting Tasigna?**

**Tasigna may not be right for you. Before taking Tasigna, tell your doctor about all of your medical conditions, including if you have:**

- heart problems
- irregular heartbeat
- QTc prolongation or a family history of it
- liver problems
- had pancreatitis
- low blood levels of potassium or magnesium in your blood
- a severe problem with lactose (milk sugar) or other sugars. The Tasigna capsules contain lactose. Most patients who have mild or moderate lactose intolerance can take Tasigna.
- had a surgical procedure involving the removal of the entire stomach (total gastrectomy)
- are pregnant or plan to become pregnant. Tasigna may harm your unborn baby. If you are able to become pregnant, you should use effective birth control during treatment with Tasigna. Talk to your doctor about the best birth control methods to prevent pregnancy while you are taking Tasigna.
- are breastfeeding or plan to breastfeed. It is not known if Tasigna passes into your breast milk. You and your doctor should decide if you will take Tasigna or breastfeed. You should not do both.

**Tell your doctor about all the medicines you take**, including prescription and non prescription medicines, vitamins and herbal supplements.

Tasigna can interact with many medicines and supplements and increase your chance for serious and life-threatening side effects. See "What is the most important information I should know about Tasigna?"

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

### **How should I take Tasigna?**

- Take Tasigna exactly as your doctor tells you to take it. Do not change your dose or stop taking Tasigna unless your doctor tells you.
- Tasigna is a long-term treatment.
- Your doctor will tell you how many Tasigna capsules to take and when to take them.
- **Do not take Tasigna with food. Take Tasigna at least 2 hours after you eat and at least 1 hour before you eat.**
- Swallow Tasigna capsules whole with water. If you cannot swallow Tasigna capsules whole, tell your doctor.
- Do not drink grapefruit juice, eat grapefruit, or take supplements containing grapefruit extract at any time during treatment. See “What is the most important information I should know about Tasigna?”
- If you miss a dose, just take your next dose as scheduled. Do not make up for a missed dose.
- If you take too much Tasigna, call your doctor or poison control center right away. Symptoms may include vomiting and drowsiness. During treatment with Tasigna your doctor will do tests to check for side effects and to see how well Tasigna is working for you. The tests will check your:
  - heart
  - blood cells (white blood cells, red blood cells, and platelets). Your blood cells should be checked every two weeks for the first two months and then monthly.
  - electrolytes (potassium, magnesium)
  - pancreas and liver function
  - bone marrow samples
- Your doctor may change your dose. Your doctor may have you stop Tasigna for some time or lower your dose if you have side effects with it.

### **What are the possible side effects of Tasigna?**

#### **Tasigna may cause serious side effects including:**

- See “What is the most important information I should know about Tasigna?”
- **Low blood counts.** Low blood counts are common with Tasigna. Your doctor will check your blood counts regularly during treatment with Tasigna. Symptoms of low blood counts include:
  - unexplained bleeding or bruising
  - blood in urine or stool
  - unexplained weakness
- **Liver damage.** Symptoms include yellow skin and eyes.

- **Pancreas inflammation (pancreatitis).** Symptoms include sudden stomach area pain with nausea and vomiting.
- **Bleeding in the brain:** Symptoms include sudden headache, changes in your eyesight, not being aware of what is going on around you and becoming unconscious.

**The most common side effects of Tasigna include:**

- low blood count
- rash
- nausea
- fever
- headache
- itching
- tiredness
- stomach (abdominal) pain
- diarrhea
- constipation
- muscle and joint pain
- back pain
- muscle spasms
- weakness
- hair loss
- runny or stuffy nose, sneezing, sore throat
- cough

Tell your doctor if you have any side effect that bothers you or does not go away.

These are not all of the possible side effects of Tasigna. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store Tasigna?**

- Store Tasigna at room temperature, 59° to 86°F (15° to 30°C).
- Safely throw away medicine that is out of date or no longer needed.
- **Keep Tasigna and all medicines out of the reach of children.**

**General information about Tasigna**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Tasigna for a condition for which it was not prescribed. Do not give Tasigna to other people, even if they have the same problem you have. It may harm them.

This Medication Guide summarizes the most important information about Tasigna. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Tasigna that is written for healthcare professionals.

For more information, go to [www.us.tasigna.com](http://www.us.tasigna.com) or call 1-866-411-8274.

**What are the ingredients in Tasigna?**

Active ingredient: nilotinib

Inactive ingredients: colloidal silicon dioxide, crospovidone, lactose monohydrate, magnesium stearate and poloxamer 188.

The capsule shell contains gelatin, titanium dioxide (E171), iron oxide yellow (E172) and iron oxide black or iron oxide red for stamping of the imprint (E172).

**This Medication Guide has been approved by the U.S. Food and Drug Administration.**

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