

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, 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 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

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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). 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).

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	<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

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	<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
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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	<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 return 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 return 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 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). Patients should also refrain from taking St. John's Wort. If patients must be co-administered a strong CYP3A4 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.

5.7 Drug Interactions

The administration of Tasigna with agents that are strong CYP3A4 inhibitors or prolonged QT 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), and Drug Interactions (7.2)].

5.8 Food Effects

The bioavailability of nilotinib is increased with food. Tasigna should 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

Tasigna has not been investigated in patients with hepatic impairment. Clinical studies have excluded patients with ALT and/or AST >2.5 (or >5, if related to disease) times the upper limit of the normal range and/or total bilirubin >1.5 times the upper limit of the normal range. Metabolism of nilotinib is mainly hepatic. Caution is recommended in patients with hepatic impairment. These patients should be closely monitored for QT interval prolongation. [See Boxed Warning, Dosage and Administration (2) and Use in Specific Populations (8.7)].

5.10 Lactose

Since the capsules contain lactose, Tasigna is not recommended for patients with rare hereditary problems of galactose intolerance, severe lactase deficiency or of glucose-galactose malabsorption.

5.11 Pregnancy

Pregnancy Category D

Tasigna can cause fetal harm when administered to a pregnant woman.

Nilotinib was studied for effects on embryo-fetal development in pregnant rats (GD 6-17) and rabbits (GD 7-20) given oral doses of 10, 30, 100 mg/kg/day, and 30, 100, 300 mg/kg/day, respectively. In rats, nilotinib at doses of 100 mg/kg/day (approximately 5.7 fold the AUC in patients at the recommended human dose) was associated with maternal toxicity (decreased gestation weight, gravid uterine weight, net weight gain, and food consumption). Nilotinib at doses ≥30 mg/kg/day 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.

There are no adequate and well controlled studies with Tasigna in pregnant women. Women should be advised to avoid becoming pregnant. 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.

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 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.

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 and Warnings and Precautions (5)].

QT prolongation and Sudden Deaths [See Boxed Warning, Warnings and Precautions (5.2, 5.3)]

Myelosuppression [See Warnings and Precautions (5.1)]

Elevated serum lipase [See Warnings and Precautions (5.4)]

Hepatotoxicity [See Warnings and Precautions (5.5)]

Electrolyte abnormalities [See Boxed Warning and 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.

In the single open-label multicenter clinical trial, a total of 438 patients were treated (CML-CP=318; CML-AP=120).

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 drug-related adverse 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 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.

Sudden deaths and QT prolongation were reported. [See Boxed Warning and Warnings and Precautions (5.2 and 5.3)].

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

Table 4 shows the percentage of patients experiencing treatment-emergent adverse reactions (excluding laboratory abnormalities) regardless of relationship to study drug. Adverse reactions reported in at least 10% of patients who received at least one dose of Tasigna are listed.

Table 4. Treatment-Emergent Adverse Reactions Reported in ≥10% of Patients in the Clinical Study^a

Body System and Preferred Term	CML-CP N=318		CML-AP N=120		
	All Grades (%)	CTC Grades ^b 3/4 (%)	All Grades (%)	CTC Grades ^b 3/4 (%)	
Skin and subcutaneous tissue disorders	Rash	33	2	28	0
	Pruritus	29	1	20	0
Gastrointestinal disorders	Nausea	31	1	18	<1
	Diarrhea	22	3	19	2
	Constipation	21	<1	18	0
	Vomiting	21	<1	10	0
Nervous system disorders	Abdominal pain	11	1	13	3
	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	Arthralgia	18	2	16	0
	Myalgia	14	2	14	<1
	Pain in extremity	13	1	16	2
	Bone pain	11	<1	13	<1
	Muscle spasms	11	<1	14	0
	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

^a Excluding laboratory abnormalities

^b NCI Common Terminology Criteria for Adverse Events, Version 3.0

Table 5 shows the percentage of patients experiencing treatment-emergent Grade 3/4 laboratory abnormalities in patients who received at least one dose of Tasigna.

Table 5. Incidence of Clinically Relevant Grade 3/4 Laboratory Abnormalities

	CML-CP N=318	CML-AP N=120
	Grades 3/4*	Grades 3/4*
Hematologic Parameters		
Thrombocytopenia	28% ¹	37% ²
Neutropenia ²	28%	37% ³
Anemia	8%	23%
Biochemistry Parameters		
Elevated lipase	15%	17%
Hyperglycemia	11%	4%
Hypophosphatemia	10%	10%
Elevated bilirubin (total)	9%	10%
Elevated SGPT (ALT)	4%	2%
Hyperkalemia	4%	3%
Hyponatremia	3%	3%
Hypokalemia	1%	5%
Elevated SGOT (AST)	1%	1%
Decreased albumin	1%	1%
Hypocalcemia	1%	4%
Elevated alkaline phosphatase	1%	3%
Elevated creatinine	<1%	0%

*NCI Common Terminology Criteria for Adverse Events, version 3.0

¹CML-CP: Thrombocytopenia: 11% were grade 3, 17% were grade 4

²CML-AP: Thrombocytopenia: 7% were grade 3, 30% were grade 4

³CML-AP: Neutropenia: 12% were grade 3, 25% were grade 4

6.2 Additional Data from Clinical Trials

The following drug-related adverse reactions are ranked under a heading of frequency, the most frequent first using the following convention: common (1%-10%), and uncommon (0.1%-1%) adverse reactions single events are captured as unknown frequency. For laboratory abnormalities, very common events ($\geq 1/10$) not included in Table 4 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: *Uncommon:* pneumonia, urinary tract infection, gastroenteritis, pharyngitis. *Unknown frequency:* sepsis, bronchitis, herpes simplex, candidiasis.

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

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

Metabolism and Nutrition Disorders: *Common:* hypomagnesemia, hyperkalemia, hyperglycemia, anorexia. *Uncommon:* hypokalemia, hyponatremia, hypocalcemia, hypophosphatemia, dehydration, decreased appetite, increased appetite. *Unknown frequency:* diabetes mellitus, hypercalcemia, hyperphosphatemia.

Psychiatric Disorders: *Common:* Insomnia. *Uncommon:* depression, anxiety. *Unknown frequency:* disorientation, confusional state.

Nervous System Disorders: *Common:* dizziness, paresthesia. *Uncommon:* intracranial hemorrhage, migraine, tremor, hypoesthesia, hyperesthesia. *Unknown frequency:* brain edema, loss of consciousness, optic neuritis, peripheral neuropathy.

Eye Disorders: *Uncommon:* eye hemorrhage, visual acuity reduced, periorbital edema, conjunctivitis, eye irritation, dry eye. *Unknown frequency:* papilloedema, diplopia, vision blurred, photophobia, eye swelling, blepharitis, eye pain.

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

Cardiac Disorders: *Common:* palpitations, electrocardiogram QT prolonged. *Uncommon:* cardiac failure, angina pectoris, atrial fibrillation, pericardial effusion, coronary artery disease, cardiomegaly, cardiac murmur, bradycardia. *Unknown frequency:* myocardial infarction, ventricular dysfunction, pericarditis, cardiac flutter, extrasystoles.

Vascular Disorders: *Common:* hypertension, flushing. *Uncommon:* hypertensive crisis, hematoma. *Unknown frequency:* shock hemorrhagic, hypotension, thrombosis.

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

Gastrointestinal Disorders: *Common:* abdominal discomfort, dyspepsia, flatulence. *Uncommon:* pancreatitis, gastrointestinal hemorrhage, melena, abdominal distension, mouth ulceration, gastroesophageal reflux, stomatitis, dry mouth. *Unknown frequency:* gastrointestinal ulcer perforation, retroperitoneal hemorrhage, hematemesis, gastric ulcer, esophagitis ulcerative, subileus.

Hepatobiliary Disorders: *Uncommon:* hepatitis. *Unknown frequency:* hepatotoxicity, hepatomegaly, jaundice.

Skin and Subcutaneous Tissue Disorders: *Common:* night sweats, eczema, urticaria, alopecia, erythema, hyperhidrosis, dry skin. *Uncommon:* exfoliative rash, ecchymosis, swelling face. *Unknown frequency:* erythema nodosum, skin ulcer, petechiae, photosensitivity.

Musculoskeletal and Connective Tissue Disorders: *Common:* musculoskeletal chest pain, musculoskeletal pain. *Uncommon:* muscular weakness. *Unknown frequency:* arthritis, joint swelling.

Renal and Urinary Disorders: *Uncommon:* dysuria, micturition urgency, nocturia, pollakiuria. *Unknown frequency:* renal failure, hematuria, urinary incontinence.

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

General Disorders and Administration Site Conditions: *Common:* pyrexia. *Uncommon:* chest pain, face edema, gravitational edema, influenza-like illness, chills, malaise.

Investigations: *Very common:* lipase increased. *Common:* blood amylase increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, blood alkaline phosphatase increased, gamma-glutamyltransferase increased, blood creatinine phosphokinase increased, blood glucose increased, weight decreased, weight increased. *Uncommon:* blood lactate dehydrogenase increased, blood glucose decreased, blood creatinine increased, blood urea increased. *Unknown frequency:* troponin increased, blood potassium decreased, blood bilirubin unconjugated 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 addition, single-dose administration of Tasigna with midazolam (a CYP3A4 substrate) to healthy subjects increased midazolam exposure by 30%. Caution should be exercised when co-administering Tasigna with substrates for these enzymes that have a narrow therapeutic index. Since warfarin is metabolized by CYP2C9 and CYP3A4 it should be avoided if possible.

In vitro studies also suggest that nilotinib may induce CYP2B6, CYP2C8 and CYP2C9, and thereby has the potential to decrease the concentrations of drugs which are eliminated by these enzymes.

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

7.2 Drugs that Inhibit or Induce Cytochrome P450 3A4 Enzymes

Nilotinib undergoes metabolism by CYP3A4, and concomitant administration of strong inhibitors or inducers of CYP3A4 can increase or decrease nilotinib concentrations significantly.

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. [See Box Warning and Warnings and Precautions (5.7)].

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 Inhibit Drug Transport Systems

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D [See Warnings and Precautions (5.11)].

8.3 Nursing Mothers

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

8.4 Pediatric Use

Safety and effectiveness of Tasigna in pediatric patients have not been established.

8.5 Geriatric Use

In the single clinical study of Tasigna, approximately 30% of patients were 65 or over. CML-CP: There was no difference in major cytogenetic response rate between patients aged <65 years and those ≥ 65 years. 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 single clinical trial, patients with a history of uncontrolled or significant cardiovascular disease were excluded [See Boxed Warning and Warnings and Precautions (5.2)].

8.7 Hepatic Impairment

Tasigna has not been investigated in patients with hepatic impairment. Caution is recommended in patients with hepatic impairment [See Boxed Warning, Dosage and Administration (2) and Warnings and Precautions (5.9)].

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

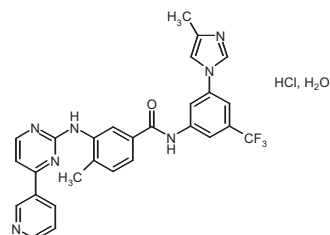
No cases of overdose have been reported. In the event of overdose, the patient should be observed and appropriate supportive treatment given.

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 565.98. 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 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), 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 Ph+ CML patients. 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) and c-Kit (210 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 of 400 mg twice daily dosing at steady state was 35% higher than with 800 mg once daily dosing. 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.

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.

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 Clinical Studies (14)].

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

Carcinogenicity studies 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 recommended human dose) or 300 mg/kg in rabbits (approximately one-half the AUC in patients at the recommended human dose). 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 recommended human dose) 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

A single open label multicenter study was conducted to evaluate the efficacy and safety of Tasigna 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 CML-CP and all CML-AP patients 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 ≥600 mg/day in 77% of all patients with 44% of patients receiving imatinib doses ≥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 6.

Table 6. Efficacy of Tasigna in CML

Cytogenetic Response Rate (Unconfirmed) (%) ^a	Chronic Phase n=232
Major (95% CI)	40% (33,46)
Complete (95% CI)	28% (22,34)
Partial (95% CI)	12% (8,16)
Accelerated Phase n=105	
Hematologic Response Rate (95% CI) ^b	
Complete Hematologic Response Rate (95% CI)	26% (18,35)
No Evidence of Leukemia (95% CI)	18% (11,27)
	8% (3,15)

^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 × 10⁹/L, platelets <450,000/mm³, 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 ≥1.5 × 10⁹/L, platelets ≥100 × 10⁹/L, no myeloblasts in peripheral blood, myeloblasts <5% in bone marrow, and no extramedullary involvement. NEL: same criteria as for CHR but neutrophils ≥1.0 × 10⁹/L and platelets ≥20 × 10⁹/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.

In this study of imatinib-resistant or intolerant CML patients, 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%). No episodes of torsade de pointes were observed in clinical studies. [See Boxed Warning, Warnings and Precautions (5.2) and Clinical Pharmacology (12.4)].

16 HOW SUPPLIED/STORAGE AND HANDLING

Tasigna (nilotinib) capsules are light yellow opaque hard gelatin capsules, size 0 with the red axial imprint "NVR/TKI." Tasigna capsules are supplied in blister packs. Blisters of 28 capsulesNDC 0078-0526-51 Each blister pack contains 2 blister cards of 14 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, 200 mg, 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)].

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* (5.11) 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.

17.5 Medication Guide

TASIGNA® (ta-sig-na)

(nilotinib)

Capsules

Read the Medication Guide that comes with Tasigna® before you start using it and each time you get a refill. There may be new information. This Medication Guide 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 heart beat, which may lead to sudden death.

Your doctor should check your heart with a test called an "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.**

Take Tasigna:

- 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 blood levels of Tasigna in your body.

- **avoid taking other medicines or supplements with Tasigna that can also cause QTc prolongation.**
 - Tell your doctor about all of the medicines you take including prescription medicines, over-the-counter medicines, vitamins and herbal supplements. Tasigna can interact with many medicines and supplements and increase your chance for serious and life-threatening side effects.

- Know the medicines you take. Keep a list of your medicines with you to show to your doctor and pharmacist. 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 faint or have an irregular heartbeat while taking Tasigna. These can be symptoms of QTc prolongation.

What is Tasigna?

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

- are no longer benefiting from another treatment, including treatment with imatinib (Gleevec®)
 - have taken other treatments and cannot tolerate them
- Tasigna has not been studied in children.

What should I tell my doctor before starting Tasigna?

Tell your doctor about all of your health problems, including if you:

- have any heart problems
- have an irregular heart beat
- have QTc prolongation or a family history of it
- have liver problems
- have had pancreatitis
- have low blood levels of potassium or magnesium
- have a severe problem with lactose (milk sugar) or other sugars.

The Tasigna capsules contain lactose.

Tell your doctor if you are pregnant or planning to become pregnant. Tasigna can harm a fetus (unborn baby).

- Women who can get pregnant must use effective birth control during treatment with Tasigna.

Tell your doctor if you are breast-feeding. Women should not breast-feed while taking Tasigna.

How should I take Tasigna?

- Take Tasigna exactly as your doctor has prescribed. Do not stop taking Tasigna or change your dose of Tasigna unless told to do so by your doctor.
- Tasigna should be taken twice a day, with about 12 hours between the two doses.
- **Do NOT take Tasigna with food. Take Tasigna at least 2 hours after any food and then wait at least 1 hour before eating again.**
- Swallow Tasigna capsules whole with water.
- Do not open Tasigna capsules.
- Do not drink grapefruit juice, eat grapefruit, or take supplements containing grapefruit extract. It may affect the levels of Tasigna in the blood.
- If you miss a dose, take your next dose as scheduled. Do not take a double dose to make up for a missed dose.
- If you take too much Tasigna, call your doctor or poison control center right away.
- Your doctor will check your heart, do regular blood tests and take bone marrow samples during treatment with Tasigna. These are done to check for side effects with Tasigna and to see how well Tasigna is working for you.
- Your doctor may have you stop Tasigna for some time or reduce your dose if you have side effects with it.

What are the possible side effects of Tasigna?

Possible Serious side effects include:

- **QTc Prolongation.** (See "What is the most important information I should know about Tasigna?") Symptoms can include an irregular heart beat and fainting.
- **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.
- **Fluid retention** including fluid build-up around the heart or lungs. Symptoms include:
 - shortness of breath
 - swelling of hands, ankles, feet, or face
- **Pancreas inflammation (pancreatitis).** Symptoms include sudden stomach area pain with nausea and vomiting.

Call your doctor right away if you have any of the above problems or symptoms while taking Tasigna.

The most common side effects of Tasigna include:

- low blood count
- rash
- nausea
- headache
- itching
- tiredness
- diarrhea
- constipation

How should I store Tasigna?

- Store Tasigna at room temperature, 59° to 86°F (15° to 30°C).
- Do not use Tasigna after the expiration date which is stated on the carton after EXP. The expiration date refers to the last day of that month.
- **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 highlights 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 written for healthcare professionals.
- For more information call 1-866-411-TASIGNA (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 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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