

**RISK EVALUATION & MITIGATION STRATEGY (REMS)**

Title:	Risk Evaluation & Mitigation Strategy (REMS)
Product Name:	Tasigna (nilotinib) NDA 022068
Sponsor:	Novartis Pharmaceuticals One Health Plaza East Hanover, NJ 07936-1080  Oncology Drug Regulatory Affairs 862 778 7414
Date:	March 1, 2010

**RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

**I. GOAL(S):**

The goals of the REMS are to:

- Minimize the occurrence of QT prolongation and its potential cardiac sequelae.
- Reduce medication errors involving drug-food interactions and incorrect dosing intervals.
- Minimize potential interactions (drug-drug and disease-drug).
- Inform patients about the serious risks associated with Tasigna treatment.
- Inform healthcare providers about the serious risks associated with the use of Tasigna, including QT prolongation.

## II. REMS ELEMENTS

### A. Medication Guide

Novartis will ensure that a Medication Guide is dispensed with each prescription of Tasigna and in accordance with 21CFR 208.24.

The Medication Guide is part of the REMS and is appended.

### B. Communication Plan

Novartis will conduct the following Communication Plan.

- 1) Within 3 months of approval of the REMS and quarterly thereafter, Novartis will hand deliver and discuss educational materials with likely Tasigna prescribers; that is, the approximately 6,000 US prescribers who treat patients for chronic myelogenous leukemia (CML).
- 2) Where access to the likely prescriber is not available for hand delivery of the materials, the materials will be delivered to the likely prescriber by shipment;
- 3) In cases of shipment of materials, Novartis will attempt to make direct follow-up contact with the prescriber to discuss the REMS materials;
- 4) Each kit of educational materials will consist of the following elements
  - a) Dear Healthcare Professional “REMS Introductory Letter”
  - b) Tasigna Educational Materials
    - i) Tasigna (nilotinib) Safety and Administration Brochure
    - ii) Patient Education Resource Kit Tasigna (nilotinib)
      - (1) Medication Guide
      - (2) Tasigna (nilotinib) Important Information about Tasigna Brochure
      - (3) Drug Timing Dial
      - (4) Medication Wallet Card

The materials listed above are part of the REMS, and are appended.

### C. Timetable for Submission of Assessments

REMS assessments will be submitted to the FDA at 18 months, 3 years, and 7 years from the date of the approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Novartis will submit each assessment so that it will be received by the FDA on or before the due date.

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## REMS Attachment. Medication Guide

### TASIGNA<sup>®</sup> (ta-sig-na) (nilotinib) Capsules

Read this Medication Guide before you start taking Tasigna<sup>®</sup> 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 no longer benefiting from another treatment, including treatment with imatinib

(Gleevec<sup>®</sup>)

- have taken other treatments 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.

**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.

- **Do not become pregnant while taking Tasigna.**

**Tell your doctor if you are breast-feeding or plan to breast-feed.** It is not known if Tasigna passes into your breast milk. You and your doctor should decide if you will take Tasigna or breast-feed. You should not do both.

**Tasigna and many other medicines may affect each other, causing serious side effects.**

See “What is the most important information I should know about Tasigna?” Tasigna may affect the way other medicines work, and other medicines may affect how Tasigna works. 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.

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- Your doctor will tell you how many Tasigna 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. Do not open Tasigna capsules. 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, 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.
  - During treatment with Tasigna your doctor will check for side effects 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?**

See “What is the most important information I should know about Tasigna?”

- **Tasigna may cause serious side effects including: 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 your 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.

- **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 and vomiting
- headache
- itching
- tiredness
- diarrhea
- constipation

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 conditions that are not mentioned 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 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 red for stamping of the imprint (E172).

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

REV: AUGUST 2009

T2009-95/T2009-96

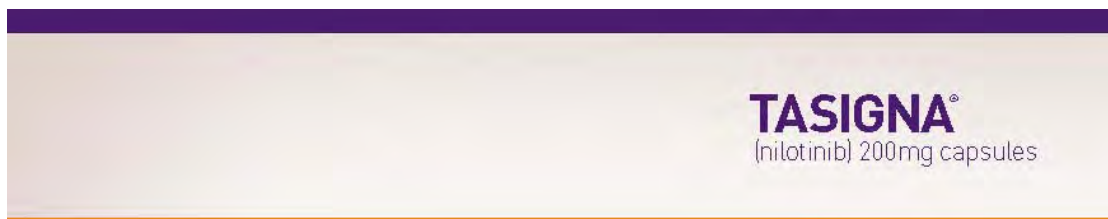
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East Hanover, New Jersey 07936

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Attachment. Educational Materials

***Dear Healthcare Professional “REMS Introductory Letter”***



DATE

Dear Healthcare Professional,

You have prescribed TASIGNA for your patients with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML). TASIGNA is indicated for the treatment of chronic phase and accelerated phase Ph+ CML in adult patients resistant or intolerant to prior therapy that included Gleevec® (imatinib mesylate) tablets. The effectiveness of TASIGNA is based on hematologic and cytogenetic response rates. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

TASIGNA is associated with serious risks including QT prolongation and sudden death. Novartis Oncology, the maker of both Gleevec and TASIGNA, is committed to educating you and your patients about these risks, as well as proper dosing and administration with TASIGNA.

That's why we are pleased to present you with the **TASIGNA Physician and Patient Educational Materials** kit. This kit is part of a communication plan developed to support the TASIGNA Risk Evaluation Mitigation Strategies (REMS). This plan is intended to help educate you and your patients on the serious risks associated with TASIGNA, as well as other safety considerations.

The kit includes the following materials:

- The **TASIGNA Safety and Administration Brochure** contains information on the serious risks of TASIGNA, including QT prolongation and sudden death, as well as the monitoring, dosing and administration, and drug/food interactions of TASIGNA. We ask that you please review this information carefully with your patients.
- The following 4 pieces are intended for your patients. We ask that you review these pieces with your patients who are taking TASIGNA. Ensuring that your patients understand the safety profile and proper dosing and administration of TASIGNA will help you address the risk of severe adverse reactions:
  - **Patient Medication Guide Brochure**
  - **Medication Wallet Card**
  - **Important Information About TASIGNA Brochure**
  - **Drug Timing Dial**

**To receive additional copies of any of these materials, please**

- Speak to your TASIGNA Sales Specialist
- Call the **TASIGNA Product Information** line at 1-866-411-TASIGNA

**For more information about TASIGNA, visit [www.us.TASIGNA.com](http://www.us.TASIGNA.com).**

With best regards,

Novartis Oncology

Please see Important Safety Information, including **Boxed WARNING**, within this letter and enclosed full Prescribing Information.

AM7-800093-C

**TASIGNA<sup>®</sup>**  
(nilotinib) 200mg capsules

## TASIGNA<sup>®</sup> (nilotinib) capsules—Important Safety Information

### 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. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

### WARNING: QT PROLONGATION AND SUDDEN DEATHS

**TASIGNA prolongs the QT interval. Sudden deaths have been reported in patients receiving nilotinib. TASIGNA should not be used in patients with hypokalemia, hypomagnesemia, or long QT syndrome. Hypokalemia or hypomagnesemia must be corrected prior to TASIGNA administration and should be periodically monitored. Drugs known to prolong the QT interval and strong CYP3A4 inhibitors should be avoided. Patients should avoid food 2 hours before and 1 hour after taking dose. A dose reduction is recommended in patients with hepatic impairment. ECGs should be obtained to monitor the QTc at baseline, seven days after initiation, and periodically thereafter, as well as following any dose adjustments.**

### CONTRAINDICATIONS

Do not use in patients with hypokalemia, hypomagnesemia, or long QT syndrome.

### WARNINGS AND PRECAUTIONS

#### Myelosuppression

Treatment with TASIGNA 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.

#### QT Prolongation

TASIGNA prolongs the QT interval. ECGs should be performed at baseline, seven days after initiation, periodically as clinically indicated, and following dose adjustments. Correct hypokalemia or hypomagnesemia prior to administration and monitor periodically.

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. The presence of hypokalemia and hypomagnesemia may further enhance this effect.

#### Sudden Deaths

There were sudden deaths reported in the safety population and in the expanded access program. Ventricular repolarization abnormalities may have contributed to their occurrence.

#### Elevated Serum Lipase

Caution is recommended in patients with a history of pancreatitis. Check serum lipase levels monthly or as clinically indicated.

**TASIGNA**<sup>®</sup>  
(nilotinib) 200mg capsules

### Important Safety Information (continued)

#### **Hepatotoxicity**

##### Serum bilirubin and hepatic transaminases

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.

#### **Electrolyte Abnormalities**

TASIGNA can cause hypophosphatemia, hypokalemia, hyperkalemia, hypocalcemia, and hyponatremia. Correct electrolyte abnormalities prior to initiating TASIGNA and monitor periodically during therapy.

#### **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 and QT interval should be monitored closely.

#### **Drug Interactions**

The concomitant use of QT prolonging drugs and strong inhibitors or inducers of CYP3A4 should be avoided as they may affect serum concentration of TASIGNA.

##### Concomitant strong CYP3A4 inhibitors

The concomitant use of 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, halofantrine, clarithromycin, haloperidol, methadone, moxifloxacin, bepridil, 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, and a dose reduction to ½ the daily dose is recommended (400 mg once daily). If the strong inhibitor is discontinued, a washout period should be allowed before TASIGNA 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. Grapefruit products and other foods that are known to inhibit CYP3A4 should also be avoided.

##### Concomitant strong CYP3A4 inducers

The concomitant use of strong CYP3A4 inducers should be avoided (including, but not limited to, 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 TASIGNA dose should be reduced to the indicated TASIGNA dose. TASIGNA is a competitive inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2D6, and UGT1A1. 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 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. Caution should be exercised when co-administering TASIGNA with substrates for these enzymes that have a narrow therapeutic index. TASIGNA inhibits human P-glycoprotein. If TASIGNA is administered with drugs that are substrates of Pgp, increased concentrations of the substrate are likely and caution should be exercised.

#### **Food Effects**

Food increases blood levels of TASIGNA. Patients should avoid food 2 hours before and at 1 hour after the dose is taken.

**TASIGNA**<sup>®</sup>  
(nilotinib) 200mg capsules

### Important Safety Information (continued)

#### 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.

#### 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. Women of child-bearing potential should avoid becoming pregnant while taking TASIGNA and should be advised of the potential hazard to the fetus if they do.

#### ADVERSE REACTIONS

In chronic phase patients, the most commonly reported adverse reactions (>10%) were rash (33%), pruritus (29%), nausea (31%), fatigue (28%), headache (31%), constipation (21%), diarrhea (22%), and vomiting (21%). The most common (>10%) Grade 3/4 adverse reactions were thrombocytopenia (28%), neutropenia (28%), elevated lipase (15%), and hyperglycemia (11%). In accelerated phase patients, the most commonly reported adverse reactions (>10%) were rash (28%), pruritus (20%), and constipation (18%). The most common (>10%) Grade 3/4 adverse reactions were thrombocytopenia (37%), neutropenia (37%), anemia (23%), and elevated lipase (17%). Other serious adverse reactions included pneumonia, febrile neutropenia, leukopenia, intracranial hemorrhage, and pyrexia (Grade 3/4: 2%).

#### DOSE ADJUSTMENTS OR MODIFICATIONS

TASIGNA may need to be temporarily withheld and/or dose reduced for QT prolongation, hematological toxicities that are not related to underlying leukemia, clinically significant moderate or severe nonhematologic toxicities, laboratory abnormalities, or concomitant use of strong CYP3A4 inhibitors. With concomitant use of strong CYP3A4 inducers, the dose of TASIGNA may need to be increased, depending on patient tolerability.

For Grade 3 to 4 lipase elevations, dosing should be withheld, and may be resumed at 400 mg once daily.

For Grade 3 to 4 bilirubin elevations, dosing should be withheld, and may be resumed at 400 mg once daily.

#### Hepatic Impairment

If possible, consider alternative therapies. If TASIGNA must be administered to patients with hepatic impairment, a lower starting dose is recommended in patients with hepatic impairment and QT interval should be monitored. The following dose reduction should be considered:

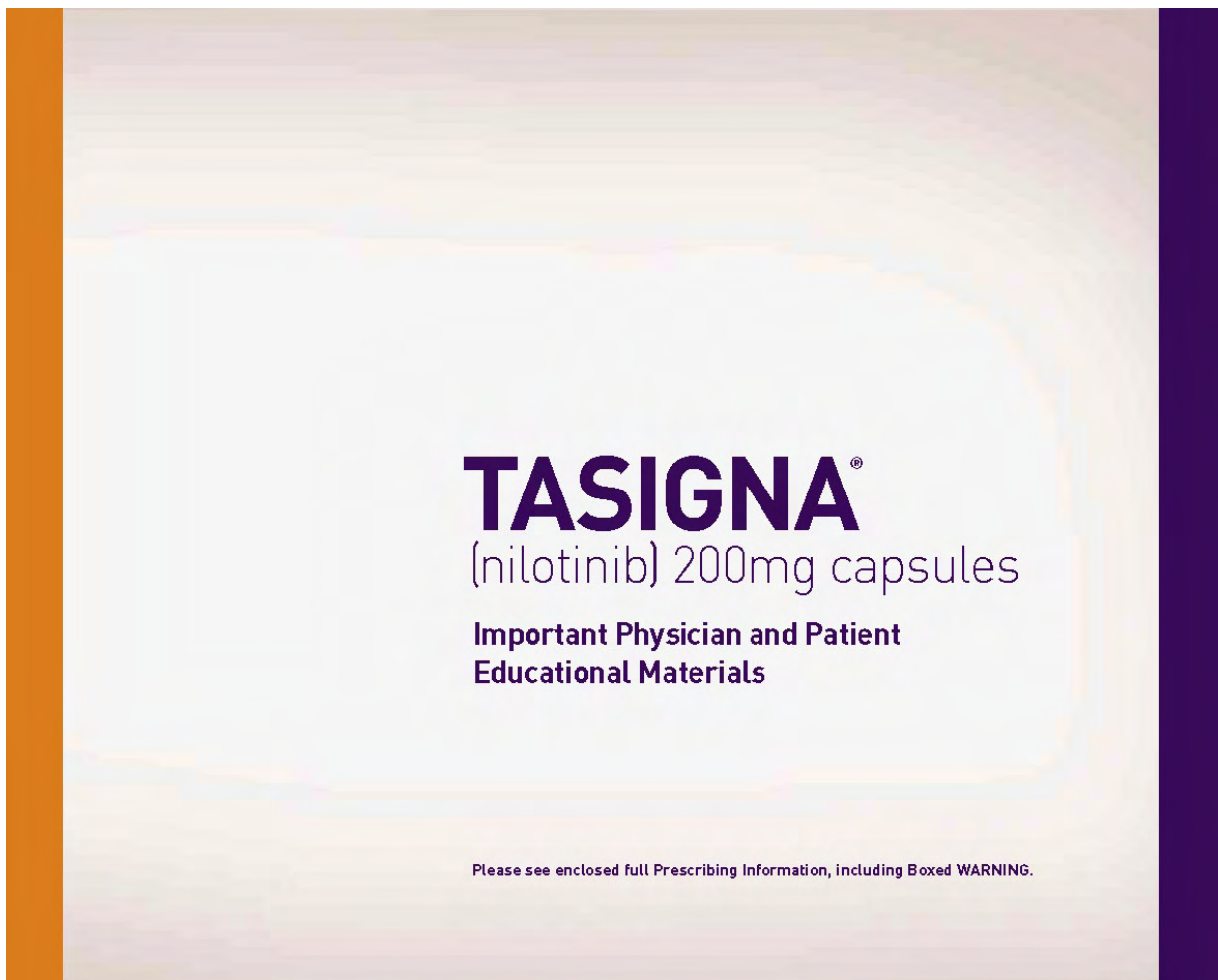
For patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, an initial dosing regimen of 400 mg in the morning and 200 mg in the evening (12 hours apart) per day followed by dose escalation to 400 mg twice daily based on patient tolerability should be considered. For patients with severe hepatic impairment (Child-Pugh Class C), a starting dose of 200 mg twice daily followed by a sequential dose escalation to 400 mg in the morning and 200 mg in the evening (12 hours apart) per day and then to 400 mg twice daily based on patient tolerability should be considered.

#### OTHER PATIENTS IN WHOM TASIGNA SHOULD BE USED WITH CAUTION

TASIGNA should not be used during pregnancy. Sexually active female patients should use effective contraception during treatment. Women should not breast feed while taking TASIGNA. The safety and effectiveness of TASIGNA in pediatric patients have not been established.

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*Tasigna (nilotinib) Important Physician and Patient Educational Materials*



**Dear Healthcare Professional,**

These **TASIGNA Important Physician and Patient Educational Materials** contain a variety of pieces to help you and your patients fully understand the serious risks associated with TASIGNA, such as QT prolongation and sudden deaths, as well as the proper dosing and administration of TASIGNA and other safety considerations. Components include:

**For Healthcare Professionals**



**Safety and Administration Brochure**

A reference tool to familiarize yourself with the serious risks associated with TASIGNA, as well as the dosing and administration guidelines, dosing adjustments and modifications, overall safety profile, and other important considerations regarding TASIGNA.

**For Patients**



**Patient Medication Guide Brochure**

Reprint of the Medication Guide contained in the TASIGNA PI. It is important to inform your patients that they should carefully read through this guide before using TASIGNA and each time they get a refill.



**Important Information About TASIGNA Brochure**

This informative brochure will help your patients understand when and how to correctly take TASIGNA. It is imperative that patients comply with this information to help address the risk of drug-drug interactions and serious adverse reactions, such as QT prolongation.



**Medication Wallet Card**

This wallet-sized card enables patients to keep a list of all their medicines. It is very important that your patients carry this card with them at all times and show it to all of their healthcare professionals. It is also crucial that they carry this card with them in case of an emergency.



**Drug Timing Dial**

A simple tool to help patients comply with the dosing schedule and food requirements of TASIGNA.

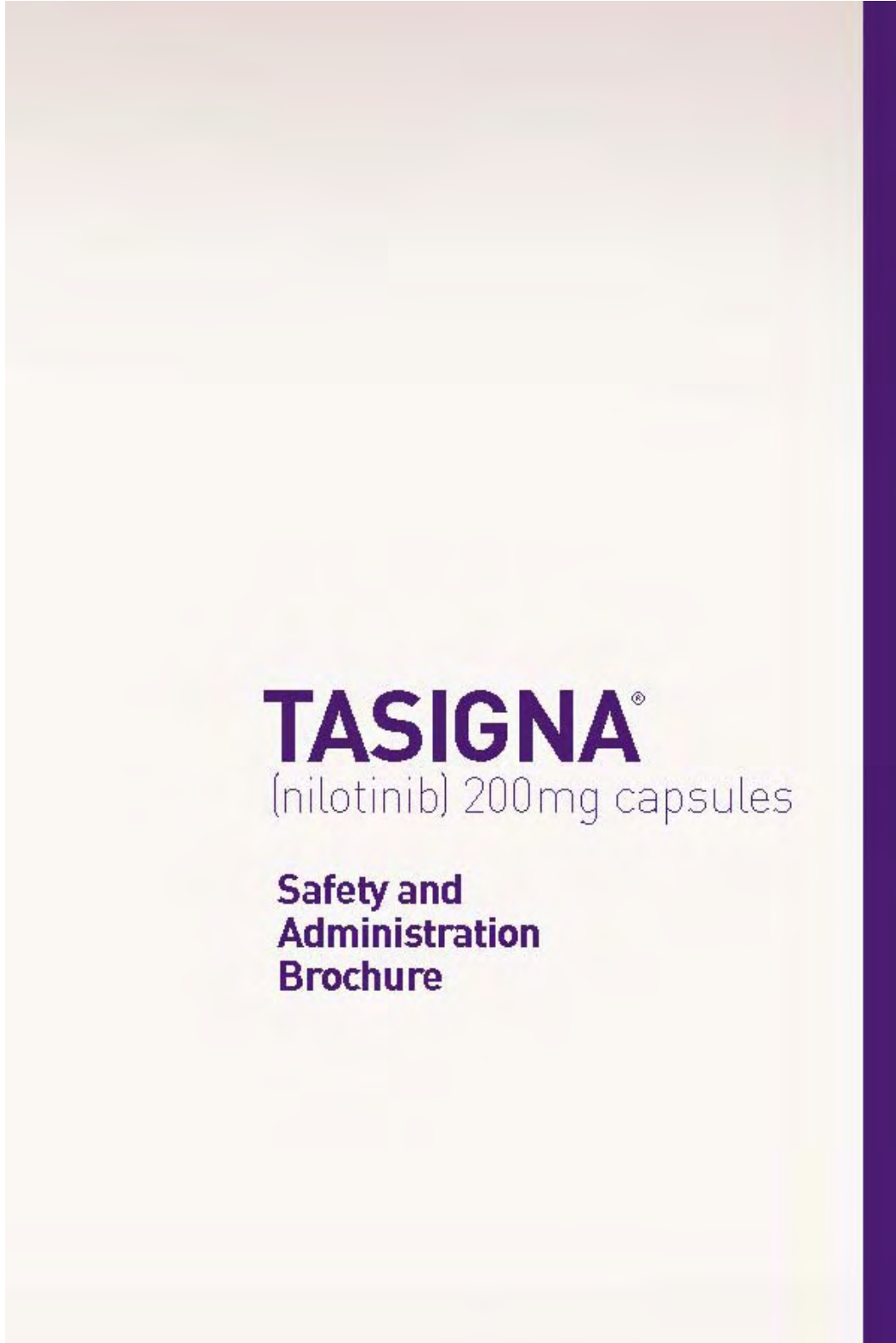
**To receive additional copies of any of these pieces, please:**

- 📞 Speak to your TASIGNA Sales Specialist
  - 📞 Call the **TASIGNA Product Information line (1-866-411-TASIGNA)**
- For more information about TASIGNA, visit [www.us.TASIGNA.com](http://www.us.TASIGNA.com)



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*Tasigna (nilotinib) Safety and Administration Brochure*



## Introduction

This **TASIGNA Safety and Administration Brochure** has been developed as part of a plan to help reduce the risk of serious adverse reactions and maximize the benefit-risk profile of TASIGNA. The purpose of this brochure is to ensure that healthcare professionals treating patients with TASIGNA:

- Understand the serious risks associated with TASIGNA, including QT prolongation and sudden death
- Understand specific drug-drug interactions, drug-food interactions, and risks associated with concomitant medical conditions
- Conduct appropriate electrocardiogram (ECG) and electrolyte monitoring for patients using TASIGNA
- Advise patients on the proper dosing of TASIGNA and the need to take TASIGNA in a fasting state

## Indication

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

## Important Warnings Regarding QT Prolongation and Sudden Deaths<sup>1</sup>

- TASIGNA prolongs the QT interval
- Sudden deaths have been reported in patients receiving TASIGNA
- TASIGNA should not be used in patients with hypokalemia, hypomagnesemia, or long QT syndrome
- Hypokalemia or hypomagnesemia must be corrected prior to TASIGNA administration and should be periodically monitored
- Drugs known to prolong the QT interval and strong CYP3A4 inhibitors should be avoided

Please see Important Safety Information, including **Boxed WARNING**, on pages 9-11 and enclosed full Prescribing Information.

- Patients should avoid food 2 hours before and 1 hour after taking dose
- A dose reduction is recommended in patients with hepatic impairment
- ECGs should be obtained to monitor the QTc at baseline, 7 days after initiation of therapy, and periodically thereafter, as well as following any dose adjustments

### Contraindications<sup>1</sup>

- Do not use in patients with hypokalemia, hypomagnesemia, or long QT syndrome

### Dosing and Administration<sup>1</sup>

- TASIGNA is supplied in a weekly dosing pack



- TASIGNA should be dosed at 400 mg twice daily. Each 200-mg capsule should be swallowed whole with water:
  - Approximately 12 hours apart
  - For example: 2 capsules in the morning and 2 capsules in the evening

### TASIGNA must not be taken with food



- Patients should not eat 2 hours before taking TASIGNA and 1 hour after taking TASIGNA
- If a dose is missed, patients should not make up the dose but should take the next dose as scheduled

## Important Considerations

### Drugs known to prolong the QT interval should be avoided<sup>2</sup>

- The following drugs have a known risk of prolonging the QT interval and their use with TASIGNA should be avoided: amiodarone, arsenic trioxide, chloroquine, chlorpromazine, clarithromycin, disopyramide, dofetilide, droperidol, erythromycin, haloperidol, ibutilide, methadone, moxifloxacin, pentamidine, pimozide, procainamide, quinidine, and sotalol. For lists of other "possible" or "conditional" risk drugs, please see the Arizona CERT at [www.azcert.org](http://www.azcert.org)

### Concomitant strong CYP3A4 inhibitors should be avoided with TASIGNA<sup>1</sup>

- The concomitant use of strong CYP3A4 inhibitors should be avoided (eg, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole)
- If treatment with any of these agents is required, it is recommended that therapy with TASIGNA be interrupted
  - If a CYP3A4 inhibitor must be coadministered, a dose reduction of TASIGNA to 400 mg once daily may be considered
  - If the strong inhibitor is discontinued, a washout period should be allowed before the TASIGNA dose is adjusted back to the indicated dose
- Foods that are known to inhibit CYP3A4, such as grapefruit and grapefruit products, may also increase serum concentrations of nilotinib and should be avoided
- Close monitoring for QT prolongation is recommended for patients who cannot avoid strong CYP3A4 inhibitors

### Concomitant strong CYP3A4 inducers should be avoided with TASIGNA<sup>1</sup>

- The concomitant use of strong CYP3A4 inducers should be avoided (eg, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital)
- Patients should also avoid St John's Wort
- If a strong CYP3A4 inducer must be coadministered, the TASIGNA dose may need to be increased, tolerability permitting
  - If the strong inducer is discontinued, TASIGNA dose should be reduced to the indicated dose

### Effects of TASIGNA on drug metabolizing enzymes and drug transport systems<sup>1</sup>

- TASIGNA is a competitive inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2D6, and UGT1A1 in vitro, potentially increasing the concentrations of drugs eliminated by these enzymes

- Caution should be exercised when coadministering TASIGNA with substrates for these enzymes, which have a narrow therapeutic index. 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
- In vitro studies also suggest that TASIGNA may induce CYP2B6, CYP2C8, and CYP2C9, and thereby has the potential to decrease the concentrations of drugs which are eliminated by these enzymes
- TASIGNA 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

#### **Drugs that inhibit drug transport systems<sup>1</sup>**

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

#### **Patients should not take TASIGNA with food<sup>1</sup>**

- The bioavailability of TASIGNA is increased with food
- Patients should not eat at least 2 hours before and at least 1 hour after taking TASIGNA
- Foods that are known to inhibit CYP3A4, such as grapefruit and grapefruit products, should be avoided

#### **Caution is recommended in patients with certain preexisting conditions<sup>1</sup>**

- 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
- 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
- Nilotinib exposure is increased in patients with impaired hepatic function. A lower starting dose is recommended for patients with mild to severe hepatic impairment, and QT interval should be monitored closely

#### **Periodic monitoring is recommended with TASIGNA<sup>1</sup>**

- For electrolyte abnormalities, such as hypokalemia, hypomagnesemia, hypophosphatemia, hyperkalemia, hypocalcemia, or hyponatremia
- For QT prolongation
  - ECGs should be obtained to monitor the QTc at baseline, 7 days after initiation of therapy, and periodically thereafter, as well as following any dose adjustments

## Important Considerations (continued)

### Pregnancy Category D<sup>1</sup>

- There are no adequate and well controlled studies with TASIGNA in pregnant women
- Women should be advised to avoid becoming pregnant while on TASIGNA

### Dose Adjustments or Modifications<sup>1</sup>

#### QT prolongation

- TASIGNA may need to be withheld and/or dose reduced for QT prolongation
- ECGs should be obtained to monitor the QT interval
  - At baseline
  - 7 days after treatment initiation and periodically thereafter
  - Following any dose adjustments

#### Dose Adjustments for QT Prolongation

##### ECGs with QTc >480 msec

- Withhold TASIGNA and perform an analysis of serum potassium and magnesium. If levels are below the lower limit of normal, correct with supplements to within normal limits. Concomitant medication use must be reviewed.
- Resume TASIGNA within 2 weeks at prior dose if QTcF returns to <450 msec and to within 20 msec of baseline.
- If QTcF is between 450 msec and 480 msec after 2 weeks, reduce the dose to 400 mg once daily.
- If, following dose reduction to 400 mg once daily, QTcF returns to >480 msec, TASIGNA should be discontinued.
- An ECG should be repeated approximately 7 days after any dose adjustment.

### Myelosuppression

- TASIGNA may need to be withheld and/or dose reduced for hematologic toxicities (neutropenia, thrombocytopenia) that are not related to the underlying leukemia

### Dose Adjustments for Neutropenia and Thrombocytopenia

<b>Chronic or Accelerated Phase CML (400 mg BID)</b>	<b>ANC* &lt;1.0x10<sup>9</sup>/L and/or platelet counts &lt;50x10<sup>9</sup>/L</b>	<ol style="list-style-type: none"> <li>Withhold TASIGNA and monitor blood counts.</li> <li>Resume within 2 weeks at prior dose if ANC &gt;1.0x10<sup>9</sup>/L and platelets &gt;50x10<sup>9</sup>/L.</li> <li>If blood counts remain low for more than 2 weeks, reduce the dose to 400 mg once daily.</li> </ol>
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\*ANC=absolute neutrophil count.

### Nonhematologic laboratory abnormalities

- TASIGNA may need to be withheld and/or dose reduced for nonhematologic laboratory abnormalities

### Dose Adjustments for Selected Nonhematologic Laboratory Abnormalities

<b>Elevated serum lipase or amylase (≥Grade 3)</b>	<ol style="list-style-type: none"> <li>Withhold TASIGNA and monitor serum lipase or amylase.</li> <li>Resume treatment at 400 mg once daily if serum lipase or amylase return to ≤Grade 1.</li> </ol>
<b>Elevated bilirubin (≥Grade 3)</b>	<ol style="list-style-type: none"> <li>Withhold TASIGNA and monitor bilirubin.</li> <li>Resume treatment at 400 mg once daily if bilirubin returns to ≤Grade 1.</li> </ol>
<b>Elevated hepatic transaminases (≥Grade 3)</b>	<ol style="list-style-type: none"> <li>Withhold TASIGNA and monitor hepatic transaminases.</li> <li>Resume treatment at 400 mg once daily if hepatic transaminases return to ≤Grade 1.</li> </ol>

## Dose Adjustments or Modifications<sup>1</sup> (continued)

- Serum lipase levels should be tested monthly or as clinically indicated
- Bilirubin and hepatic transaminases levels should be tested monthly or as clinically indicated

### Hepatic Impairment

- If possible, consider alternative therapies. If TASIGNA must be administered to patients with hepatic impairment, the following dose reduction should be considered:
  - For patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, an initial dosing regimen of 400 mg in the morning and 200 mg in the evening (12 hours apart) per day followed by dose escalation to 400 mg twice daily based on patient tolerability should be considered
  - For patients with severe hepatic impairment (Child-Pugh Class C), a starting dose of 200 mg twice daily followed by a sequential dose escalation to 400 mg in the morning and 200 mg in the evening (12 hours apart) per day and then to 400 mg twice daily based on patient tolerability should be considered

### Other nonhematologic toxicities

- If other clinically significant moderate or severe nonhematologic toxicity develops, dosing should be withheld, but may be resumed at 400 mg once daily when the toxicity has resolved
- Dose escalation to 400 mg BID should be considered, if clinically appropriate

## TASIGNA Patient Resources

- The **TASIGNA Patient Medication Guide Brochure** provides FDA-approved language to help you educate your patients about
  - Important safety information, including possibly serious side effects with TASIGNA
  - The proper dosing and administration of TASIGNA
- The **Important Safety Information about TASIGNA Brochure** is also available to help you educate your patients. This brochure focuses on the dosing and administration requirements for TASIGNA
- The **TASIGNA Product Information line (1-866-411-TASIGNA)** is also available to address requests for additional information about TASIGNA

## TASIGNA® (NILETINIB) CAPSULES - IMPORTANT SAFETY INFORMATION

### 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. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

#### WARNING: QT PROLONGATION AND SUDDEN DEATHS

TASIGNA prolongs the QT interval. Sudden deaths have been reported in patients receiving nilotinib. TASIGNA should not be used in patients with hypokalemia, hypomagnesemia, or long QT syndrome. Hypokalemia or hypomagnesemia must be corrected prior to TASIGNA administration and should be periodically monitored. Drugs known to prolong the QT interval and strong CYP3A4 inhibitors should be avoided. Patients should avoid food 2 hours before and 1 hour after taking dose. A dose reduction is recommended in patients with hepatic impairment. ECGs should be obtained to monitor the QTc at baseline, seven days after initiation, and periodically thereafter, as well as following any dose adjustments.

### CONTRAINDICATIONS

Do not use in patients with hypokalemia, hypomagnesemia, or long QT syndrome.

### WARNINGS AND PRECAUTIONS

#### Myelosuppression

Treatment with TASIGNA 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.

#### QT Prolongation

TASIGNA prolongs the QT interval. ECGs should be performed at baseline, seven days after initiation, periodically as clinically indicated, and following dose adjustments. Correct hypokalemia or hypomagnesemia prior to administration and monitor periodically.

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. The presence of hypokalemia and hypomagnesemia may further enhance this effect.

#### Sudden Deaths

There were sudden deaths reported in the safety population and in the expanded access program. Ventricular repolarization abnormalities may have contributed to their occurrence.

#### Elevated Serum Lipase

Caution is recommended in patients with a history of pancreatitis. Check serum lipase levels monthly or as clinically indicated.

#### Hepatotoxicity

##### Serum bilirubin and hepatic transaminases

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.

#### Electrolyte Abnormalities

TASIGNA can cause hypophosphatemia, hypokalemia, hyperkalemia, hypocalcemia, and hyponatremia. Correct electrolyte abnormalities prior to initiating TASIGNA and monitor periodically during therapy.

#### 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 and QT interval should be monitored closely.

#### Drug Interactions

The concomitant use of QT prolonging drugs and strong inhibitors or inducers of CYP3A4 should be avoided as they may affect serum concentration of TASIGNA.

##### Concomitant strong CYP3A4 inhibitors

The concomitant use of 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, halofantrine, clarithromycin, haloperidol, methadone, moxifloxacin, bepridil, 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, and a dose reduction to ½ the daily dose is recommended (400 mg once daily). If the strong inhibitor is discontinued, a washout period should be allowed before TASIGNA 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. Grapefruit products and other foods that are known to inhibit CYP3A4 should also be avoided.

##### Concomitant strong CYP3A4 inducers

The concomitant use of strong CYP3A4 inducers should be avoided (including, but not limited to, 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 TASIGNA dose should be reduced to the indicated TASIGNA dose. TASIGNA is a competitive inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2D6, and UGT1A1. 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 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. Caution should be exercised when co-administering TASIGNA with substrates for these enzymes that have a narrow therapeutic index. TASIGNA inhibits human P-glycoprotein. If TASIGNA is administered with drugs that are substrates of Pgp, increased concentrations of the substrate are likely and caution should be exercised.

#### Food Effects

Food increases blood levels of TASIGNA. Patients should avoid food 2 hours before and at 1 hour after the dose is taken.

#### 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.

#### 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. Women of child-bearing potential should avoid becoming pregnant while taking TASIGNA and should be advised of the potential hazard to the fetus if they do.

#### ADVERSE REACTIONS

In chronic phase patients, the most commonly reported adverse reactions (>10%) were rash (33%), pruritus (29%), nausea (31%), fatigue (28%), headache (31%), constipation (21%), diarrhea (22%), and vomiting (21%). The most common (>10%) Grade 3/4 adverse reactions were thrombocytopenia (28%), neutropenia (28%), elevated lipase (15%), and hyperglycemia (11%). In accelerated phase patients, the most commonly reported adverse reactions (>10%) were rash (28%), pruritus (20%), and constipation (18%). The most common (>10%) Grade 3/4 adverse reactions were thrombocytopenia (37%), neutropenia (37%), anemia (23%), and elevated lipase (17%). Other serious adverse reactions included pneumonia, febrile neutropenia, leukopenia, intracranial hemorrhage, and pyrexia (Grade 3/4: 2%).

#### DOSE ADJUSTMENTS OR MODIFICATIONS

TASIGNA may need to be temporarily withheld and/or dose reduced for QT prolongation, hematological toxicities that are not related to underlying leukemia, clinically significant moderate or severe nonhematologic toxicities, laboratory abnormalities, or concomitant use of strong CYP3A4 inhibitors. With concomitant use of strong CYP3A4 inducers, the dose of TASIGNA may need to be increased, depending on patient tolerability.

For Grade 3 to 4 lipase elevations, dosing should be withheld, and may be resumed at 400 mg once daily. For Grade 3 to 4 bilirubin elevations, dosing should be withheld, and may be resumed at 400 mg once daily.

#### Hepatic impairment

If possible, consider alternative therapies. If TASIGNA must be administered to patients with hepatic impairment, a lower starting dose is recommended in patients with hepatic impairment and QT interval should be monitored. The following dose reduction should be considered:

For patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, an initial dosing regimen of 400 mg in the morning and 200 mg in the evening (12 hours apart) per day followed by dose escalation to 400 mg twice daily based on patient tolerability should be considered. For patients with severe hepatic impairment (Child-Pugh Class C), a starting dose of 200 mg twice daily followed by a sequential dose escalation to 400 mg in the morning and 200 mg in the evening (12 hours apart) per day and then to 400 mg twice daily based on patient tolerability should be considered.

#### OTHER PATIENTS IN WHOM TASIGNA SHOULD BE USED WITH CAUTION

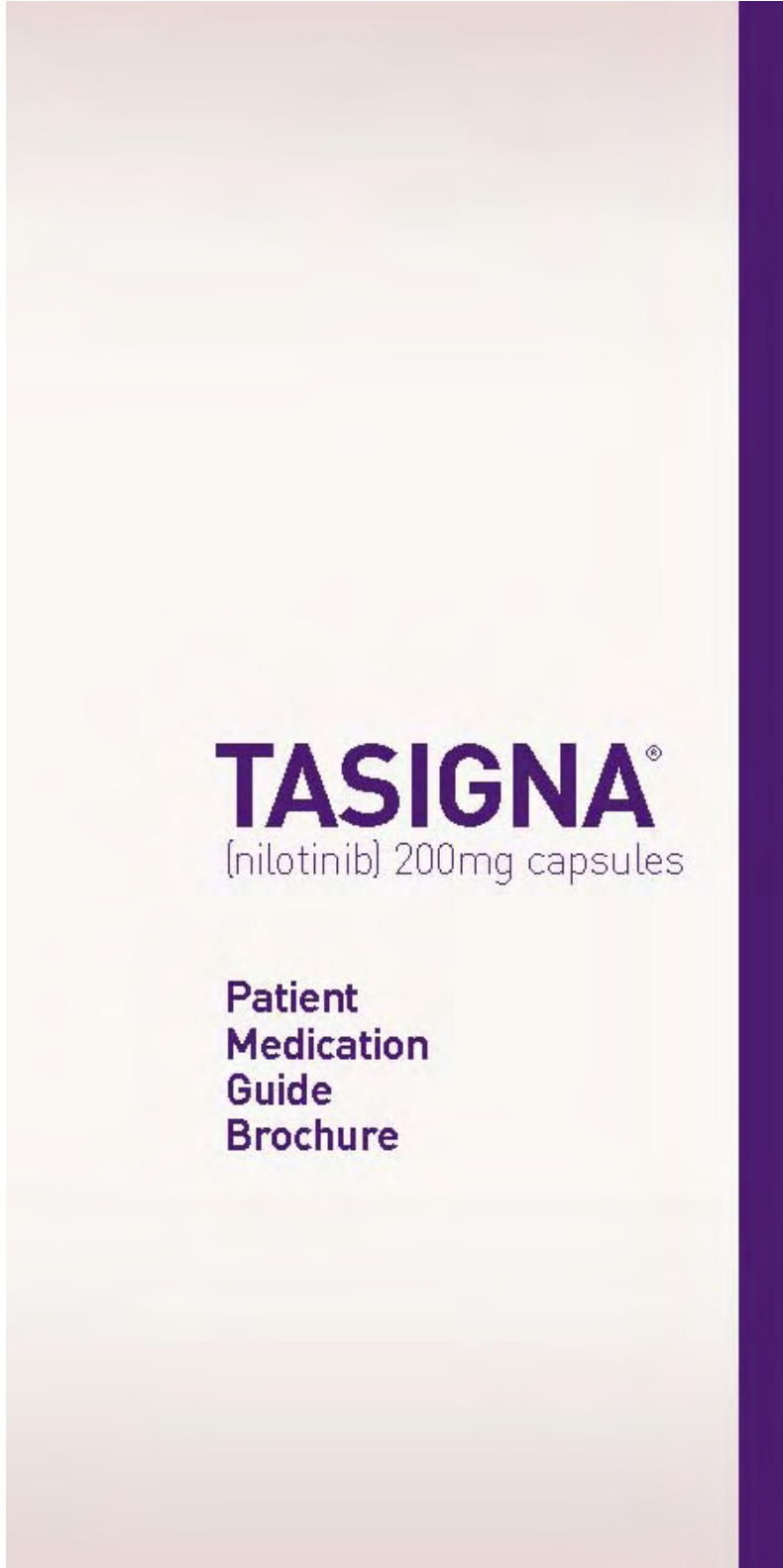
TASIGNA should not be used during pregnancy. Sexually active female patients should use effective contraception during treatment. Women should not breast feed while taking TASIGNA. The safety and effectiveness of TASIGNA in pediatric patients have not been established.

References: 1. TASIGNA® (nilotinib) capsules prescribing information. East Hanover, NJ: Novartis Pharmaceuticals Corporation; Aug 2009. 2. Arizona Center for Education and Research on Therapeutics (CERT). QT drug lists by risk groups. <http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm>. Accessed March 25, 2009.



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**Tasigna (nilotinib) Patient Medication Guide Brochure**



## 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 no longer benefiting from another treatment, including treatment with imatinib (Gleevec®)
- have taken other treatments 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.

**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.

- **Do not become pregnant while taking Tasigna.**

**Tell your doctor if you are breast-feeding or plan to breast-feed.** It is not known if Tasigna passes into your breast milk. You and your doctor should decide if you will take Tasigna or breast-feed. You should not do both.

**Tasigna and many other medicines may affect each other, causing serious side effects.** See "What is the most important information I should know about Tasigna?" Tasigna may affect the way other medicines work, and other medicines may affect how Tasigna works.

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 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. Do not open Tasigna capsules. 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, 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.
- During treatment with Tasigna your doctor will check for side effects 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?

See "What is the most important information I should know about Tasigna?"

- **Tasigna may cause serious side effects including: 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 your 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.
- **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 and vomiting
- headache
- itching
- tiredness
- diarrhea
- constipation

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 conditions that are not mentioned 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 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 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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For more information,  
please visit [www.us.tasigna.com](http://www.us.tasigna.com)  
or call 1-866-411-Tasigna.



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## Tasigna (nilotinib) Important Information About Tasigna Brochure

**TASIGNA<sup>®</sup>**  
(nilotinib) 200mg capsules

**Important  
Information  
About TASIGNA  
Brochure**

This patient brochure is part of a number of educational tools designed to help you understand the serious risks associated with taking TASIGNA, as well as how you can help minimize these risks by taking TASIGNA properly and avoiding interactions with food or other medications.

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## Important Things to Know About TASIGNA

**TASIGNA is a medicine that is available by prescription only.**

### Remember:

- TASIGNA can cause a possible life-threatening heart problem called QT prolongation
  - QT prolongation can cause an irregular heartbeat and even lead to sudden death
- Your heart should be checked with a test called an electrocardiogram (ECG) to check the electrical activity of your heart before starting treatment, 7 days after starting treatment, regularly during treatment, and after a dosage change
- Your doctor should check the levels of electrolytes (potassium and magnesium) in your blood, your blood cells (including white blood cells, red blood cells, and platelets), pancreas and liver functions, and bone marrow samples

**Please see Important Safety Information on pages 8-11 and enclosed Patient Medication Guide.**

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- You may lower your chances for QT prolongation with TASIGNA by:
  - Taking TASIGNA on an empty stomach.  
**DO NOT TAKE TASIGNA WITH FOOD**
  - Avoiding grapefruit and grapefruit products
  - Avoiding medicines that are strong CYP3A4 inhibitors (your doctor will determine if any of your medicines are strong CYP3A4 inhibitors)
  - Avoiding other medicines or supplements that can also cause QT prolongation
- Call your doctor right away if you feel lightheaded, faint, or have an irregular heartbeat while taking TASIGNA
  - These can be symptoms of QT prolongation

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### 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 adult patients who:

- Are no longer benefiting from another treatment, including treatment with imatinib (Gleevec®)
- Have taken other treatments and cannot tolerate them

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

### Can I take TASIGNA with food?



Avoid food for **at least 2 hours before** taking TASIGNA and **at least 1 hour after**.

**DO NOT TAKE TASIGNA WITH FOOD.** Food can affect the amount of TASIGNA in your body, which can lead to serious side effects. Taking TASIGNA on an empty stomach may lower your chances of having a possibly life-threatening heart problem called QT prolongation. QT prolongation causes an irregular heartbeat, which may lead to sudden death.

**Please see Important Safety Information on pages 8-11 and enclosed Patient Medication Guide.**

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**Aside from NOT eating around the time I take TASIGNA, are there any other foods or beverages I should avoid during TASIGNA therapy?**

Do not drink grapefruit juice, eat grapefruit, or take supplements containing grapefruit extract. These may affect the amount of TASIGNA in your blood, which can lead to serious side effects.



**Can I take TASIGNA with other medicines?**

Keep a list of all your medicines with you to show to your doctor and pharmacist.

Avoid taking other medicines or supplements with TASIGNA that can also cause QT prolongation.

Tell them 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 some of these interactions may increase your chance for serious and life-threatening side effects.

Do not take any other medicines while taking TASIGNA unless your doctor tells you it is okay to do so.

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### What does TASIGNA look like?

TASIGNA comes in pale yellow capsules containing 200 mg of nilotinib.



TASIGNA comes in a special package that will help you remember to take 2 capsules of TASIGNA twice a day.

### When should I take TASIGNA?

Take two 200-mg capsules twice a day as prescribed by your doctor about 12 hours apart.

For example:

- 2 capsules in the morning, swallowed whole with water
- 2 capsules in the evening, swallowed whole with water

Try to take your capsules at the same time each day.



Please see Important Safety Information on pages 8-11 and enclosed Patient Medication Guide.

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**What should I do if I forget to take TASIGNA?**

If you miss a dose, take your next dose as scheduled. Do NOT take a double dose to make up for a missed dose.

**What should I do if I take more TASIGNA than I should?**

If you take too much TASIGNA, call your doctor or poison control center right away.

**How should I store TASIGNA?**

Keep TASIGNA and all medicines out of the reach of children. 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.

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## Important Safety Information

### Important information about 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 no longer benefiting from another treatment, including treatment with imatinib (Gleevec®)
- Have taken other treatments and cannot tolerate them

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

#### **What is the most important information to know about TASIGNA?**

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

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

- Before taking TASIGNA
- 7 days after starting TASIGNA
- Regularly during treatment
- After any dose changes

#### **You may lower your chances for having QT prolongation with TASIGNA if you:**

- **Take TASIGNA on an empty stomach.**
- **DO NOT TAKE TASIGNA WITH FOOD**
  - Food can affect the levels of TASIGNA in your body, which can lead to serious side effects
  - Taking TASIGNA on an empty stomach may lower your chances of having a possibly life-threatening heart problem called QT prolongation
  - QT prolongation causes an irregular heartbeat, which may lead to sudden death

### Take TASIGNA:

- At least 2 hours after eating any food, and
- After taking TASIGNA, 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 other supplements with TASIGNA that can also cause QT prolongation**

TASIGNA is a prescription medication. TASIGNA comes in 200 mg capsules. Your doctor will prescribe 400 mg of TASIGNA to be taken twice a day for a total daily dose of 800 mg. Each dose should be taken approximately 12 hours apart. 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

### Before taking TASIGNA

Talk to your doctor or pharmacist about **all** other medication(s) you may be taking, including prescription medicines, over-the-counter medicines, vitamins, and herbal supplements, since they may affect how TASIGNA works and increase your chance of serious and life-threatening side effects.

### Tell your doctor if:

- You have a heart disorder or are taking medication for the heart
- You have an irregular heartbeat
- You have QT prolongation or a family history of it
- You have liver problems

(continued on next page)

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- You know that you suffer from low blood levels of electrolytes, such as potassium, magnesium, or calcium
- You have a pancreas disorder
- Also tell your doctor if you are pregnant, breast-feeding, or lactose-intolerant. The TASIGNA capsules contain lactose. Most patients who have mild or moderate lactose intolerance can take TASIGNA

**Call your doctor right away if you faint or have an irregular heartbeat while taking TASIGNA.**

These can be symptoms of QT prolongation.

**Call your doctor immediately if you experience any of these symptoms.**

**Serious side effects**

TASIGNA is sometimes associated with serious side effects, some symptoms of which include:

- Feeling lightheaded, fainting, or having an irregular heartbeat
- Unexplained bleeding or bruising
- Blood in urine or stool
- Unexplained weakness
- Yellow skin and eyes
- Shortness of breath
- Swelling of hands, ankles, feet, or face
- Sudden stomach area pain with nausea and vomiting
- Sudden headache, changes in your eyesight, not being aware of what is going on around you, and becoming unconscious

**Common side effects**

Most patients experience side effects at some time. Some common side effects you may experience include:

- Low blood count
- Rash
- Nausea and vomiting
- Headache
- Itching

**Please see enclosed Patient Medication Guide.**

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- Tiredness
- Diarrhea
- Constipation

Be sure to tell your doctor or pharmacist if you have any side effects during treatment with TASIGNA.

**Tell your doctor if you are pregnant or planning to become pregnant. TASIGNA can harm a fetus (unborn baby).** Women who can become pregnant must use effective birth control during treatment with TASIGNA.

- **Do not become pregnant while taking TASIGNA**

**Tell your doctor if you are breast-feeding.**

Tell your doctor if you are breast-feeding or plan to breast-feed. It is not known if TASIGNA passes into your breast milk. You and your doctor should decide if you will take TASIGNA or breast-feed, taking into account the importance of the drug. You should not breast-feed and take TASIGNA at the same time.

**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 should check your blood to monitor the amount of blood cells (white blood cells, red blood cells, and platelets) during treatment. These should be checked every two weeks for the first two months and then monthly thereafter, or as considered necessary by your doctor.

Your doctor may have you stop TASIGNA for some time or reduce your dose if you have side effects with it.

Please see accompanying patient information, including **Boxed WARNING**, and the TASIGNA Medication Guide you received with your prescription.

For more information, please visit  
[www.us.tasigna.com](http://www.us.tasigna.com) or call  
1-866-411-TASIGNA.



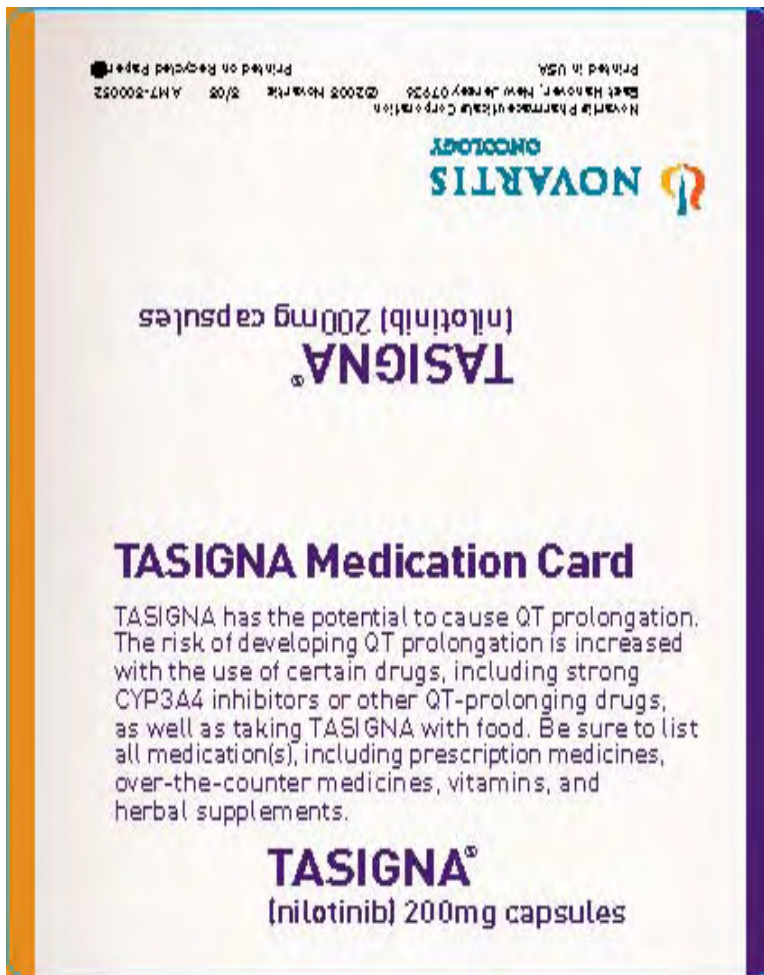
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East Hanover, New Jersey 07924

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## Drug Timing Dial



## Tasigna (nilotinib) Medication Wallet Card



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**ONCOLOGY**  
**NOVARTIS**

**TASIGNA<sup>®</sup>**  
(nilotinib) 200mg capsules

**TASIGNA Medication Card**

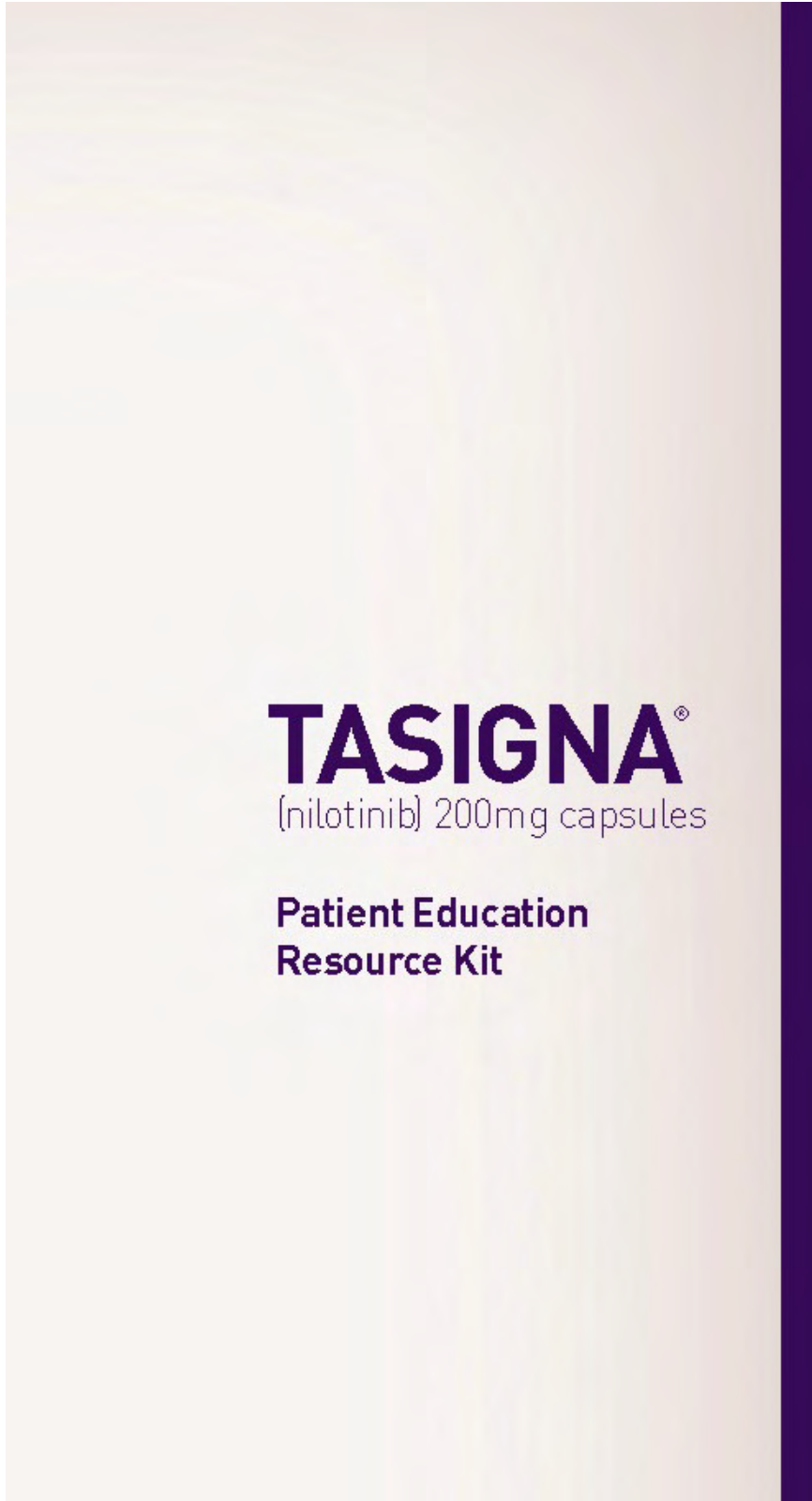
TASIGNA has the potential to cause QT prolongation. The risk of developing QT prolongation is increased with the use of certain drugs, including strong CYP3A4 inhibitors or other QT-prolonging drugs, as well as taking TASIGNA with food. Be sure to list all medication(s), including prescription medicines, over-the-counter medicines, vitamins, and herbal supplements.

**TASIGNA<sup>®</sup>**  
(nilotinib) 200mg capsules



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**Tasigna (nilotinib) Patient Education Resource Kit**



## Dear Patient,

### **The TASIGNA Patient Education Resource Kit**

contains materials that will help you understand the risks associated with taking TASIGNA, as well as the dosing and administration of TASIGNA. This kit also includes important safety information about TASIGNA. After reviewing these materials, speak with your doctor if you have any further questions or concerns about TASIGNA.

The TASIGNA Patient Education Resource Kit contains the following helpful tools:



#### **Patient Medication Guide Brochure**

This is a reprint of the Medication Guide contained in the TASIGNA Prescribing Information. You should carefully read through this before using TASIGNA and each time you get a refill.



#### **Important Information About TASIGNA Brochure**

This will help you understand when and how to correctly take TASIGNA.



### **Drug Timing Dial**

This tool will help you follow the dosing schedule and food requirements of TASIGNA.



### **Medication Wallet Card**

This wallet-sized card will help you keep a list of all your medicines. You should carry this card with you at all times and show it to your doctors and pharmacist. It is important to carry this card with you in case of an emergency.

