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:	26 Oct. 2011

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 6,900 US prescribers who treat patients for chronic myelogenous leukemia (CML). This communication plan will be in effect for two years following the approval of the January 14, 2011, modified REMS.
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) 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 initial approval of the REMS (March 15, 2010). 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.

REMS Attachment. 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.
  - If you cannot swallow Tasigna capsules whole, you may open the Tasigna capsule and sprinkle the contents of each capsule in 1teaspoon of applesauce (puréed apple). Swallow the mixtureright away (within 15 minutes). For more information, see "**How should I take Tasigna?"**

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

What is Tasigna?

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

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

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

Who should not take Tasigna?

Do not take if you have:

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

What should I tell my doctor before starting Tasigna?

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

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

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

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

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

How should I take Tasigna?

- Take Tasigna exactly as your doctor tells you to take it. Do not change your dose or stop taking Tasigna unless your doctor tells you.
- Tasigna is a long-term treatment.
- Your doctor will tell you how many Tasigna capsules to take and when to take them.

- **Do not take Tasigna with food. Take Tasigna at least 2 hours after you eat and at least 1 hour before you eat.**
- Swallow Tasigna capsules whole with water. If you cannot swallow Tasigna capsules whole:
  - Open the Tasigna capsules and sprinkle the contents in 1 teaspoon of applesauce (puréed apple).
    - Do not use more than 1teaspoon of applesauce.
    - Only useapplesauce. Do not sprinkle Tasigna onto other foods.
  - Swallow the mixture right away (within 15 minutes).
- 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 make up for a missed dose.
- If you take too much Tasigna, call your doctor or poison control center right away. Symptoms may include vomiting and drowsiness.
- During treatment with Tasigna your doctor will 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?

Tasigna may cause serious side effects including:

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

- **Pancreas inflammation (pancreatitis).** Symptoms include sudden stomach area pain with nausea and vomiting.
- **Bleeding in the brain:** Symptoms include sudden headache, changes in your eyesight, not being aware of what is going on around you and becoming unconscious.
- **Tumor Lysis Syndrome (TLS).** TLS is caused by a fast breakdown of cancer cells. TLS can cause you to have:
  - kidney failure and the need for dialysis treatment
  - an abnormal heart beat

Your doctor may do blood tests to check you for TLS.

The most common side effects of Tasigna include:

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

Tell your doctor if you have any side effect that bothers you or does not go away.
These are not all of the possible side effects of Tasigna. For more information, ask your doctor or pharmacist.

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

How should I store Tasigna?

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

General information about Tasigna

Medicines are sometimes prescribed for 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, go to www.us.tasignaTRADENAME.com or call 1-866-411-8274.

What are the ingredients in Tasigna?

- Active ingredient: nilotinib
- Inactive ingredients: colloidal silicon dioxide, crospovidone, lactose monohydrate, magnesium stearate and poloxamer 188.
- The capsule shell contains gelatin, titanium dioxide (E171), iron oxide yellow (E172) and iron oxide black or iron oxide red for stamping of the imprint (E172).

Manufactured by

Novartis Pharma Stein AG

Stein, Switzerland

Distributed by:

Novartis Pharmaceuticals Corporation

East Hanover, New Jersey 07936

Revised October 2011

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

Attachment. Educational Materials

Dear Healthcare Professional "REMS Introductory Letter"

TASIGNA®
(nilotinib) capsules
150/200mg

XXXXX 2011

Dear health care 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.

TASIGNA is also indicated for adult patients with newly diagnosed Ph+ CML in the chronic phase. The effectiveness of TASIGNA is based on major molecular response and cytogenetic response rates. The study is ongoing and further data will be required to determine long-term outcome.

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.

As part of a communication plan to support the TASIGNA Risk Evaluation Mitigation Strategies (REMS), Novartis presents the **TASIGNA Physician and Patient Education Materials** kit. This kit 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**
  - **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**

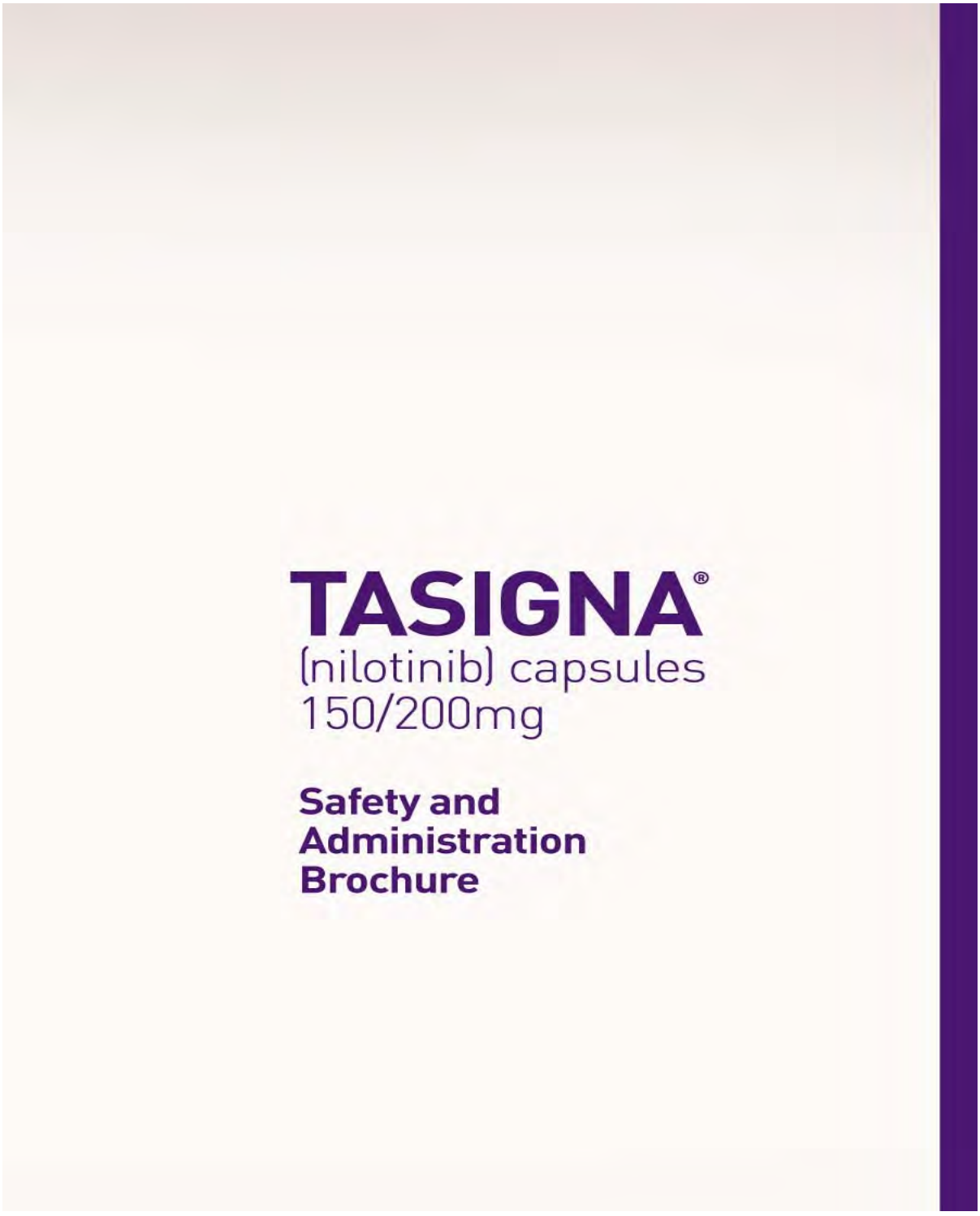
For more information about TASIGNA, visit www.us.TASIGNA.com.

With best regards,
Novartis Oncology

AM7-1003722

Tasigna (nilotinib) Important Physician and Patient Educational Materials

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. For detailed safety information, including the **Boxed WARNING**, refer to the enclosed full Prescribing Information. The purpose of this brochure is to ensure that health care 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[1]

TASIGNA (nilotinib) is indicated for the treatment of chronic phase and accelerated phase Philadelphia chromosome–positive chronic myelogenous leukemia (Ph+ CML) in adult patients resistant or intolerant to prior therapy that included imatinib. The effectiveness of TASIGNA is based on hematologic and cytogenetic response rates. TASIGNA is also indicated for the treatment of adult patients with newly diagnosed Ph+ CML in chronic phase. The effectiveness of TASIGNA is based on major molecular response and cytogenetic response rates. The study is ongoing and further data will be required to determine long-term outcome.

Important Warnings Regarding QT Prolongation and Sudden Deaths

- TASIGNA prolongs the QT interval[1]
- Sudden deaths have been reported in CML patients treated with nilotinib in clinical studies (n=5661; 0.3%). The relative early occurrence of some of these deaths relative to the initiation of TASIGNA suggests the possibility that ventricular repolarization abnormalities may have contributed to their occurrence[1]
- TASIGNA should not be used in patients with hypokalemia, hypomagnesemia, or long QT syndrome[1]

Please see enclosed full Prescribing Information.

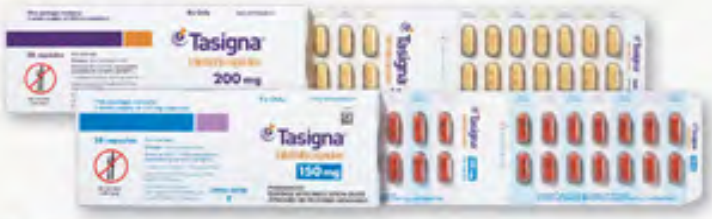
- Hypokalemia or hypomagnesemia must be corrected prior to TASIGNA administration and should be periodically monitored
- Drugs known to prolong the QT interval and strong CYP3A4 inhibitors should be avoided
- Patients should avoid food 2 hours before and 1 hour after taking dose
- A dose reduction is recommended in patients with hepatic impairment
- ECGs should be obtained to monitor the QTc at baseline, 7 days after initiation of therapy, and periodically thereafter, as well as following any dose adjustments

Contraindications[1]

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

Dosing and Administration[1]

- TASIGNA is supplied in a weekly dosing pack



- TASIGNA is available in 2 dosage strengths: 150-mg and 200-mg capsules
- The recommended dose of TASIGNA is 300 mg bid for adult patients with newly diagnosed Ph+ CML
- The recommended dose of TASIGNA is 400 mg bid for adult patients resistant or intolerant to prior therapy that included imatinib
- TASIGNA should be dosed twice daily. Capsules should be swallowed whole with water approximately 12 hours apart

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
- For patients unable to swallow capsules, the contents of each capsule may be dispersed in 1 teaspoon of applesauce (puréed apple) and should be taken immediately (within 15 minutes)
- Not more than 1 teaspoon of applesauce and no food other than applesauce may be used

3

Important Considerations

Drugs known to prolong the QT interval should be avoided[2]

- 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

Concomitant strong CYP3A4 inhibitors should be avoided with TASIGNA[1]

- 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 patients must be coadministered a strong CYP3A4 inhibitor, based on pharmacokinetic studies, consider a dose reduction to 300 mg once daily in patients with resistant or intolerant Ph+ CML or to 200 mg once daily in patients with newly diagnosed Ph+ CML-CP
  - 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[1]

- 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
- Based on the nonlinear pharmacokinetic profile of nilotinib, increasing the dose of TASIGNA when coadministered with such agents is unlikely to compensate for the loss of exposure

Proton pump inhibitors

- Since proton pump inhibitors affect pH of the upper GI tract for an extended period, separation of doses may not eliminate the interaction. The concomitant use of proton pump inhibitors with TASIGNA should be used with caution

Effects of TASIGNA on drug-metabolizing enzymes and drug transport systems[1]

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

Please see enclosed full Prescribing Information.

4

- 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 that 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[1]

- 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[1]

- 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[1]

- The use of TASIGNA can cause increases in serum lipase. Caution is recommended in patients with a previous history of pancreatitis. If lipase elevations are accompanied by abdominal symptoms, doses should be interrupted and appropriate diagnostics should be considered to exclude pancreatitis. Serum lipase should be checked periodically
- The exposure of nilotinib is reduced in patients with total gastrectomy. More frequent follow-up of these patients should be considered. Dose increase or alternative therapy may be considered in patients with total gastrectomy
- 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[1]

- 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

5

Important Considerations (continued)

Pregnancy Category D[1]

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

Dose Adjustments or Modifications[1]

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

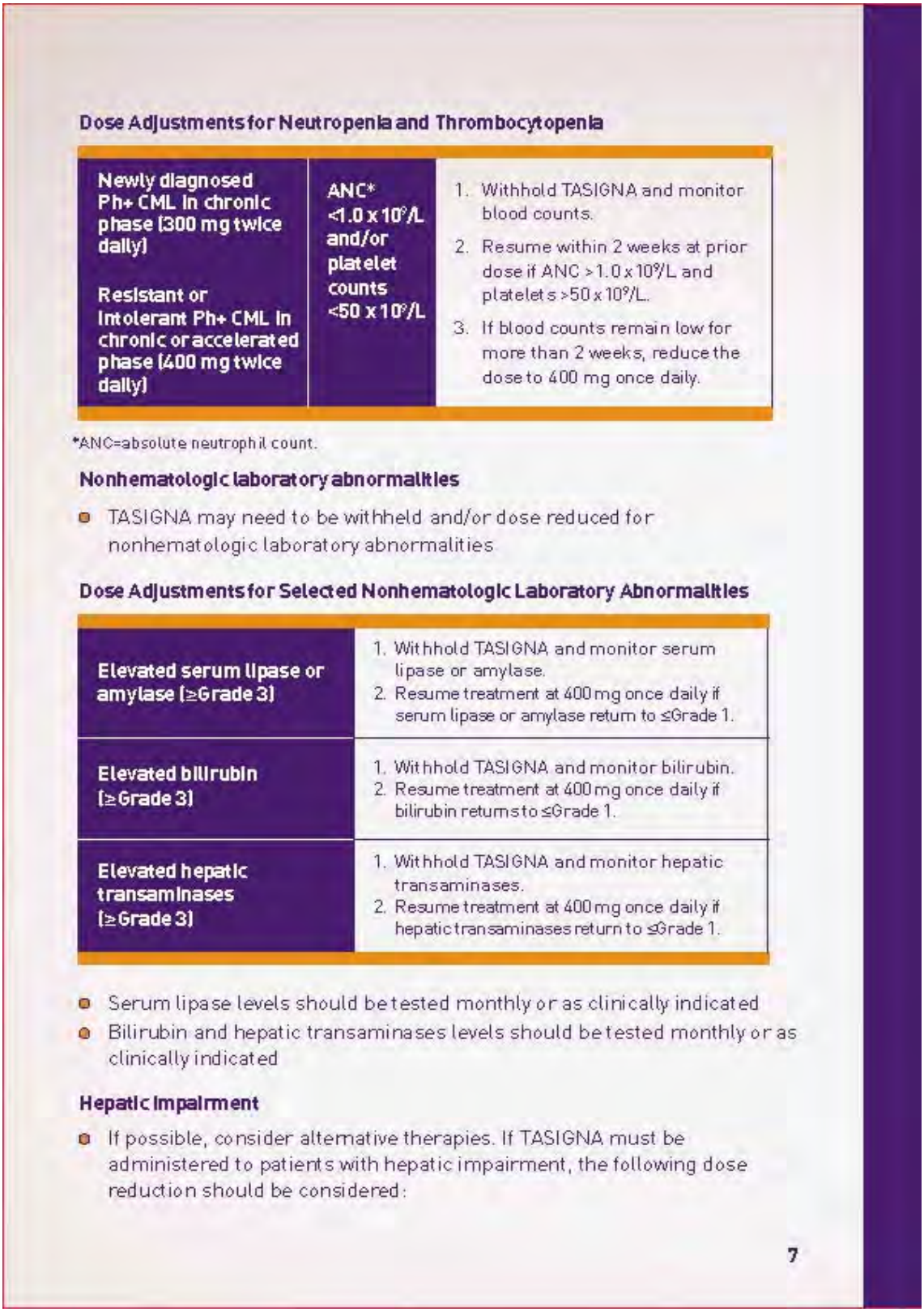
ECGs with QTc >480 msec	1. Withhold TASIGNA and perform an analysis of serum potassium and magnesium. If levels are below the lower limit of normal, correct with supplements to within normal limits. Concomitant medication use must be reviewed. 2. Resume TASIGNA within 2 weeks at prior dose if QTcF returns 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.

Myelosuppression

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

Please see enclosed full Prescribing Information.

6



Dose Adjustments for Neutropenia and Thrombocytopenia

Newly diagnosed Ph+ CML in chronic phase (300 mg twice daily) **Resistant or intolerant Ph+ CML in chronic or accelerated phase (400 mg twice daily)**	**ANC* <1.0 x 10^9/L and/or platelet counts <50 x 10^9/L**	1. Withhold TASIGNA and monitor blood counts. 2. Resume within 2 weeks at prior dose if ANC >1.0 x 10^9/L and platelets >50 x 10^9/L. 3. If blood counts remain low for more than 2 weeks, reduce the dose to 400 mg once daily.

*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

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

- 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:

7

Dose Adjustments or Modifications[1] (continued)

Newly diagnosed Ph+ CML-CP

For patients with mild (Child-Pugh Class A), moderate (Child-Pugh Class B), and severe hepatic impairment (Child-Pugh Class C), an initial dosing regimen of 200 mg twice daily followed by dose escalation to 300 mg twice daily based on tolerability should be considered.

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

For patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, an initial dosing regimen of 300 mg twice daily followed by dose escalation to 400 mg twice daily based on 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 300 mg twice daily and then to 400 mg twice daily based on 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
- If clinically appropriate, escalation of the dose to 300 mg bid or 400 mg bid should be considered

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 **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

References: 1. TASIGNA® (nilotinib) capsules prescribing information. East Hanover, NJ: Novartis Pharmaceuticals Corporation; December 2010. **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 October 15, 2010.

NOVARTIS
ONCOLOGY

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

Printed in USA 10/10 AM7-1003723 Printed on Recycled Paper

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

2

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
- If you cannot swallow TASIGNA capsules whole, you may open the TASIGNA capsules and sprinkle the contents of each capsule in 1 teaspoon of applesauce (puréed apple). Swallow the mixture right away (within 15 minutes). For more information, see **"How should I take TASIGNA?"**

3

Call your doctor right away if you feel light-headed, faint, or have an irregular heartbeat while taking TASIGNA. These can be symptoms of QTc prolongation.

What is TASIGNA?

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

- Are newly diagnosed **or**
- Are no longer benefiting from previous other treatments, including treatment with imatinib (Gleevec®), **or**
- Have taken other treatments, including imatinib (Gleevec®), 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

4

What should I tell my doctor before starting TASIGNA?

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

- Heart problems
- Irregular heartbeat
- QTc prolongation or a family history of it
- Liver problems
- Had pancreatitis
- Low blood levels of potassium or magnesium in your blood
- A severe problem with lactose (milk sugar) or other sugars. The TASIGNA capsules contain lactose. Most patients who have mild or moderate lactose intolerance can take TASIGNA
- Had a surgical procedure involving the removal of the entire stomach (total gastrectomy)
- Are pregnant or plan to become pregnant. TASIGNA may harm your unborn baby. If you are able to become pregnant, you should use effective birth control during treatment with TASIGNA. Talk to your doctor about the best birth control methods to prevent pregnancy while you are taking TASIGNA

5

- Are breastfeeding or plan to breastfeed. It is not known if TASIGNA passes into your breast milk. You and your doctor should decide if you will take TASIGNA or breastfeed. You should not do both

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

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

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

How should I take TASIGNA?

- Take TASIGNA exactly as your doctor tells you to take it. Do not change your dose or stop taking TASIGNA unless your doctor tells you
- TASIGNA is a long-term treatment
- Your doctor will tell you how many TASIGNA capsules to take and when to take them

- **Do not take TASIGNA with food. Take TASIGNA at least 2 hours after you eat and at least 1 hour before you eat**
- Swallow TASIGNA capsules whole with water. If you cannot swallow TASIGNA capsules whole, tell your doctor
- **If you cannot swallow TASIGNA capsules whole:**
  - Open the TASIGNA capsules and sprinkle the contents in 1 teaspoon of applesauce (puréed apple)
    - Do not use more than 1 teaspoon of applesauce
    - Only use applesauce. Do not sprinkle TASIGNA onto other foods
  - Swallow the mixture right away (within 15 minutes)
- Do not drink grapefruit juice, eat grapefruit, or take supplements containing grapefruit extract at any time during treatment. See "What is the most important information I should know about TASIGNA?"
- If you miss a dose, just take your next dose as scheduled. Do not make up for a missed dose

7

- If you take too much TASIGNA, call your doctor or poison control center right away. Symptoms may include vomiting and drowsiness. During treatment with TASIGNA your doctor will do tests to check for side effects and to see how well TASIGNA is working for you. The tests will check your:
  - Heart
  - Blood cells (white blood cells, red blood cells, and platelets). Your blood cells should be checked every two weeks for the first two months and then monthly
  - Electrolytes (potassium, magnesium)
  - Pancreas and liver function
  - Bone marrow samples
- Your doctor may change your dose. Your doctor may have you stop TASIGNA for some time or lower your dose if you have side effects with it

What are the possible side effects of TASIGNA?

TASIGNA may cause serious side effects, including:

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

8

- **Low blood counts.** Low blood counts are common with TASIGNA. Your doctor will check your blood counts regularly during treatment with TASIGNA. Symptoms of low blood counts include:
  - Unexplained bleeding or bruising
  - Blood in urine or stool
  - Unexplained weakness
- **Liver damage.** Symptoms include yellow skin and eyes
- **Pancreas inflammation (pancreatitis).** Symptoms include sudden stomach area pain with nausea and vomiting
- **Bleeding in the brain.** Symptoms include sudden headache, changes in your eyesight, not being aware of what is going on around you and becoming unconscious
- **Tumor Lysis Syndrome (TLS).** TLS is caused by a fast breakdown of cancer cells. TLS can cause you to have:
  - Kidney failure and the need for dialysis treatment
  - An abnormal heart beat

Your doctor may do blood tests to check you for TLS.

9

The most common side effects of TASIGNA include:

- Low blood count
- Rash
- Nausea
- Fever
- Headache
- Itching
- Tiredness
- Stomach (abdominal) pain
- Diarrhea
- Constipation
- Muscle and joint pain
- Back pain
- Muscle spasms
- Weakness
- Hair loss
- Runny or stuffy nose, sneezing, sore throat
- Cough

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

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

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

How should I store TASIGNA?

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

10

General information about TASIGNA

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

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

For more information, go to www.us.TASIGNA.com or call 1-866-411-8274.

What are the ingredients in TASIGNA?

Active ingredient: nilotinib.

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

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

11

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

REV: October 2011

Manufactured by:
Novartis Pharma Stein AG
Stein, Switzerland

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

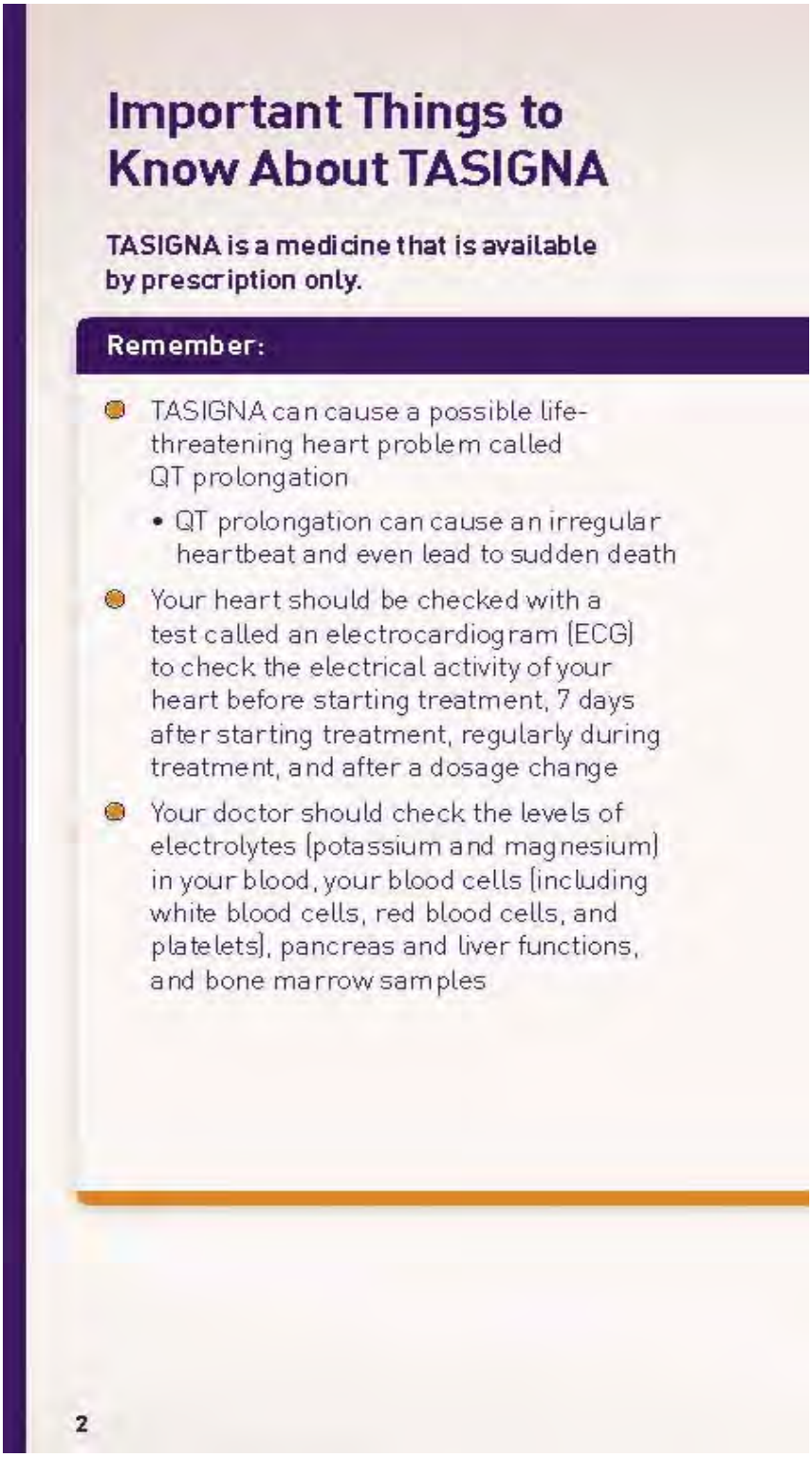
For more information,
please visit **www.us.TASIGNA.com**
or call **1-866-411-TASIGNA**.

NOVARTIS
ONCOLOGY

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

©2011 Novartis Printed in USA 10/11 AM7-1021126 Printed on Recycled Paper

Tasigna (nilotinib) Information About Tasigna Brochure


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
2


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 (vitamins) that can also cause QT prolongation
Call your doctor right away if you feel light-headed, faint, or have an irregular heartbeat while taking TASIGNA
These can be symptoms of QT prolongation
3

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 newly diagnosed
- Are no longer benefiting from previous other treatments, including treatment with imatinib (Gleevec®)
- Have taken other treatments, including imatinib (Gleevec®), 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.

4

If you cannot swallow TASIGNA capsules whole, you may open the TASIGNA capsules and sprinkle the contents of each capsule in 1 teaspoon of applesauce (puréed apple). Swallow the mixture right away (within 15 minutes). For more information, see **"If you cannot swallow TASIGNA capsules whole"** on page 7.

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 and supplements (vitamins) 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.

5

What does TASIGNA look like?

TASIGNA comes in:

1) Red capsules containing 150 mg of nilotinib
2) 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.

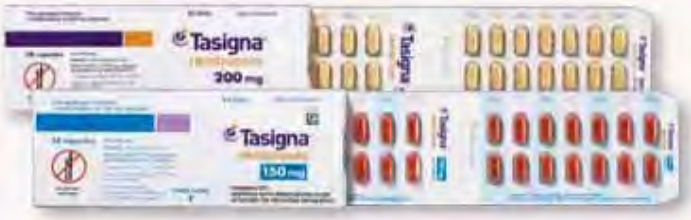
When should I take TASIGNA?

Take 2 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.



6

If you cannot swallow TASIGNA capsules whole

1) Open the TASIGNA capsules and sprinkle the contents in 1 teaspoon of applesauce (puréed apple)
   - Do not use more than 1 teaspoon of applesauce
   - Only use applesauce. Do not sprinkle TASIGNA onto other foods
2) Swallow the mixture right away (within 15 minutes)

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?

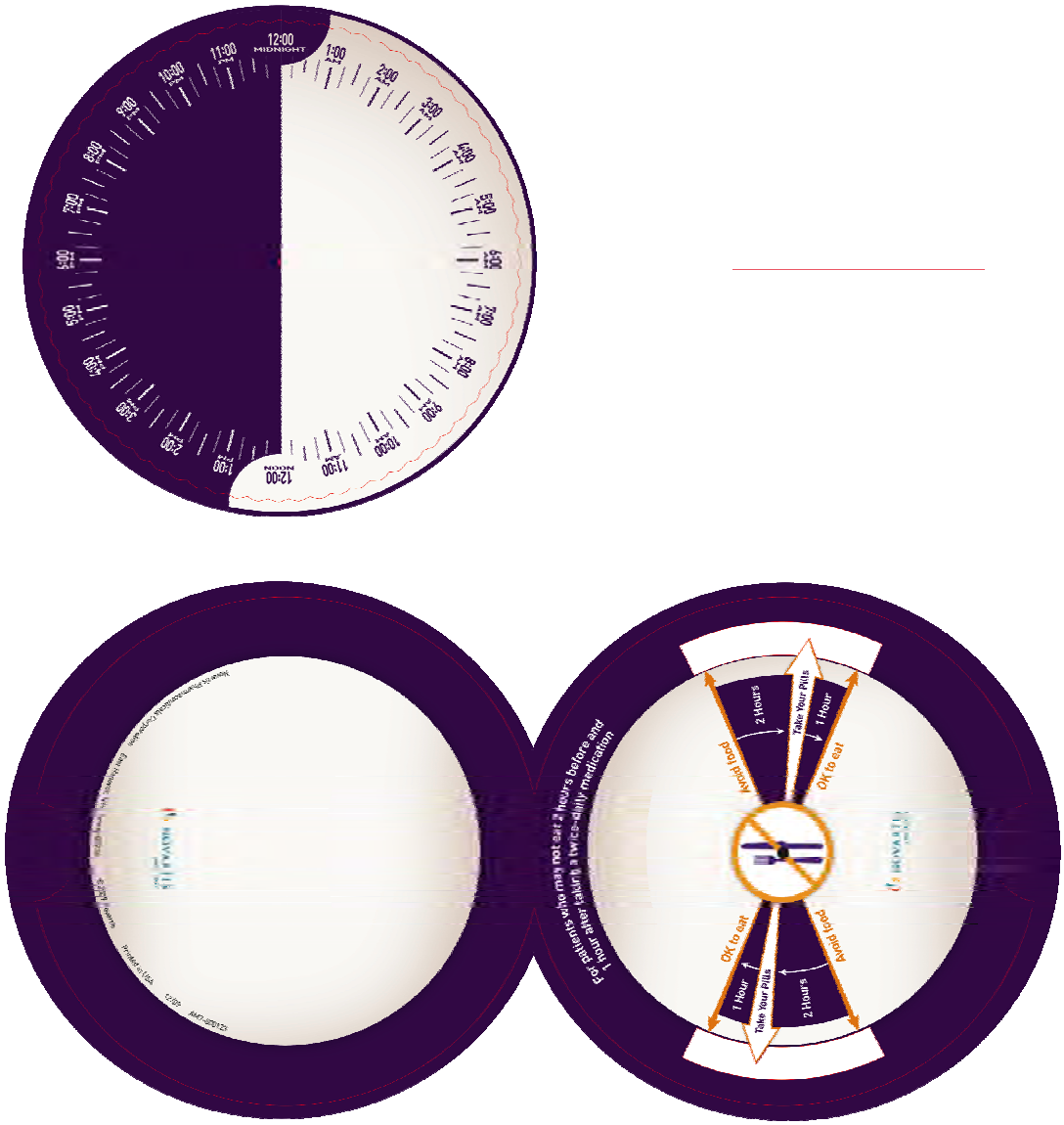
Keep TASIGNA and all medicines out of the reach of children. Store TASIGNA at room temperature, 59°F to 86°F (15°C-30°C). Safely throw away medicine that is out of date or no longer needed.

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

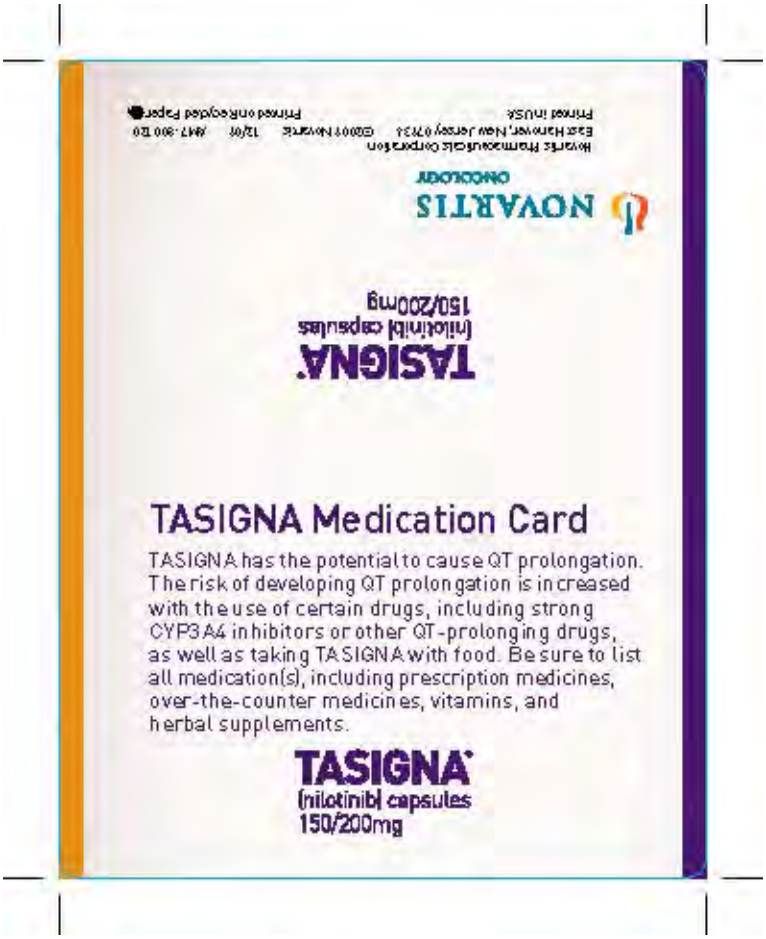
7


For more information, please visit
www.us.TASIGNA.com or call
1-866-411-TASIGNA.
NOVARTIS
ONCOLOGY
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080
©2011 Novartis
Printed in USA
1/11
AM7-1003631
Printed on Recycled Paper

Drug Timing Dial



Tasigna (nilotinib) Medication Wallet Card



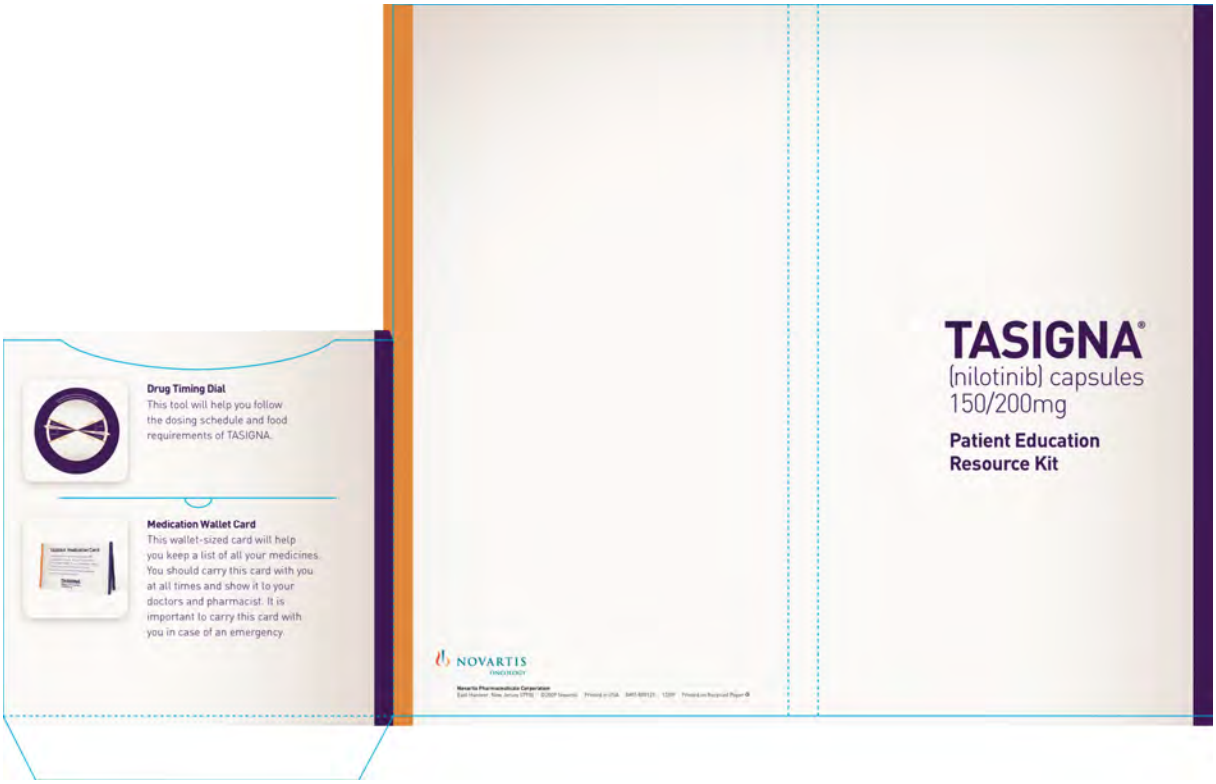
I am taking TASIGNA® (nilotinib)

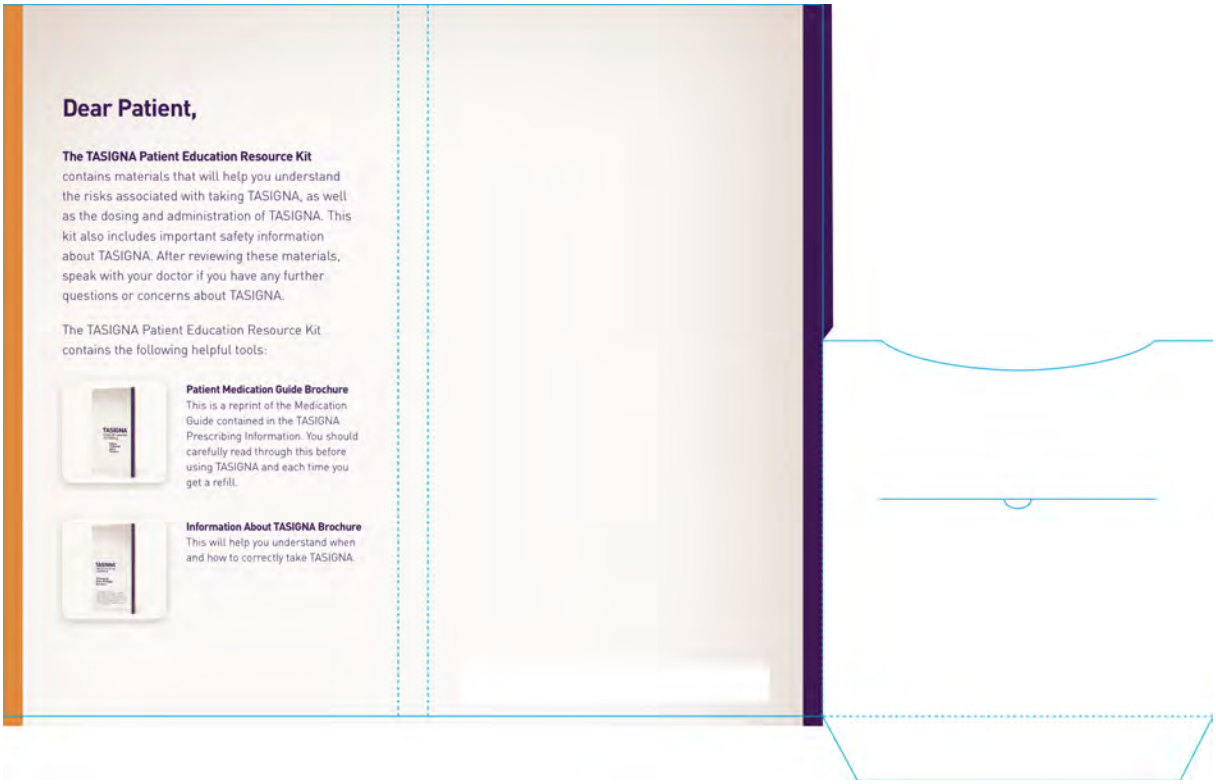
It is important to be aware of the medications I am taking, including prescription medicines, over-the-counter medicines, vitamins, and herbal supplements to avoid potentially serious adverse reactions, including QT prolongation.

I am currently on the following medication(s):

Name of medication (prescription & over-the-counter)	Dosage	Frequency	Start date

Tasigna (nilotinib) Patient Education Resource Kit





This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANN T FARRELL
11/18/2011