

# PRODUCT MONOGRAPH

**PrTASIGNA<sup>®</sup>**

(Nilotinib Capsules)

150 mg and 200 mg nilotinib (as nilotinib hydrochloride monohydrate)

Protein-tyrosine kinase inhibitor

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PrTASIGNA<sup>®</sup> (nilotinib capsules) is a registered trademark

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**PrTASIGNA®**

(nilotinib capsules)

**PART I: HEALTH PROFESSIONAL INFORMATION**

**SUMMARY PRODUCT INFORMATION**

<b>Route of Administration</b>	<b>Pharmaceutical Form/Strength</b>	<b>Clinically Relevant Nonmedicinal Ingredients</b>
Oral	Capsule 200 mg Capsule 150 mg	Capsule content: Lactose monohydrate.  <i>For a complete listing see Dosage Forms, composition and Packaging section.</i>

**INDICATIONS AND CLINICAL USE**

- TASIGNA (nilotinib capsules) is indicated for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase.

Clinical effectiveness of TASIGNA in newly diagnosed Ph+ CML-CP is based on major molecular response rate at 12 months and complete cytogenetic response rate by 12 months. As of the 60 month cut off date, no overall survival benefit has been demonstrated (see **CLINICAL TRIALS**).

- TASIGNA (nilotinib capsules) is also indicated for the treatment of chronic phase and accelerated phase Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in adult patients resistant to or intolerant of at least one prior therapy including imatinib.

Clinical effectiveness of TASIGNA in imatinib-resistant or -intolerant Ph+ CML-CP was based on the unconfirmed major cytogenetic and complete hematologic response rates. Clinical effectiveness of TASIGNA in imatinib-resistant or -intolerant Ph+ CML-AP was based on the confirmed hematologic response rates and the unconfirmed major cytogenetic response rates. (See **CLINICAL TRIALS**).

TASIGNA should only be prescribed by a qualified healthcare professional who is experienced in the use of antineoplastic therapy and in the treatment of chronic myeloid leukemia.

**Geriatrics (≥ 65 years of age) :** Approximately 12% and 30% of subjects in the clinical studies (Phase III study (A2303) in newly diagnosed Ph+ CML-CP; and Phase II study (A2101) in

resistant or -intolerant Ph+ CML-CP and CML-AP) were 65 years of age or older respectively. No major differences were observed for safety and efficacy in patients  $\geq$  65 years of age as compared to adults 18 to 65 years of age.

**Pediatrics:** Safety and efficacy in children and adolescents below the age of 18 has not been established.

## CONTRAINDICATIONS

Do not use in patients with a known long QTc prolongation or with a persistent QTc of  $>480$  msec (See **WARNINGS AND PRECAUTIONS**).

Do not use in patients with uncorrectable hypokalemia or hypomagnesemia.

Do not use in patients with known hypersensitivity to nilotinib or to any of the excipients (for a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph).

## WARNINGS AND PRECAUTIONS

### Serious Warnings and Precautions

- Sudden Cardiac Deaths (see Warnings and Precautions and Adverse Reactions)
- QT interval prolongation (see Warnings and Precautions, Drug Interactions, Food Effect and Monitoring and Laboratory Tests)
- Should not be used in patients with uncorrectable hypokalemia or hypomagnesemia (see Warnings and Precautions)
- Ischemic heart disease, ischemic cerebrovascular events and peripheral arterial occlusive disease (PAOD), (in some rare cases, fatal) (see Warnings and Precautions and Monitoring and Laboratory Tests)
- Hepatotoxicity/ Hepatic failure (in some cases, fatal) (see Warnings and Precautions)
- Pancreatitis (see Warnings and Precautions)
- Myelosuppression (thrombocytopenia, neutropenia and anemia) (see Warnings and Precautions)

TASIGNA should only be prescribed by a qualified healthcare professional who is experienced in the use of antineoplastic therapy and in the treatment of chronic myeloid leukemia.

### **BCR-ABL Mutations**

The T315I mutation confers a high level of resistance to nilotinib and most tyrosine kinase inhibitors based on *in vitro* and clinical data.

## **Sudden Cardiac Deaths**

In clinical trials, 19 cases of sudden cardiac death have been reported out of 11,351 patients receiving TASIGNA (uncommon frequency of 0.17%). Of the 19 cases, 13 documented cases had a past medical history of cardiac disease or significant cardiac risk factors for sudden cardiac death. In 4 of the 19 cases of sudden cardiac death, patients had no prior medical history of cardiac disease. Comorbidities in addition to the underlying malignancy were also frequently present as were concomitant medications. Ventricular repolarization abnormalities may have been contributory factors. No cases of sudden cardiac deaths have been reported in any treatment group in the newly diagnosed Ph+ CML-CP Phase III study (A2303). Based on post-marketing exposure in patient-years, the estimated reporting rate for spontaneous reports of sudden death is 0.02% per patient-year.

## **QT Prolongation**

*In vitro* data indicate that nilotinib has the potential to prolong cardiac ventricular repolarization (QT interval).

In the Phase III study (A2303) in newly diagnosed Ph+ CML-CP patients, the maximum QTcF mean increase from baseline was 12.3 msec in the nilotinib 300 mg twice daily arm (two-sided 90% Upper CI: 14.4) and 12.9 msec in the nilotinib 400 mg twice daily arm (two-sided 90% Upper CI: 15.1). At the recommended dose of 300 mg twice daily no patient had an absolute QTcF of >480 msec and no events of Torsades de Pointes were observed in this trial. One patient in the 400 mg twice daily arm had an absolute QTcF of >480 msec. Thirty-two (32) patients (11.5%) in nilotinib 300 mg twice daily treatment group and 40 patients (14.4%) in nilotinib 400 mg twice daily treatment group had absolute QTcF >450 msec. QTcF increase from baseline that exceeded 60 msec was observed in 5 patients while on treatment drug (one in the TASIGNA 300 mg twice daily treatment group and four in the TASIGNA 400 mg twice daily treatment group).

In the Phase II study (A2101) in imatinib-resistant or -intolerant CML patients in CP and AP, treated with nilotinib 400 mg twice daily, the change from baseline in mean time-averaged QTcF interval at steady-state was 5 msec and 8 msec, respectively. The maximum QTcF mean increase from baseline was 6.8 msec (two-sided 90% Upper CI: 8.4) and 13.4 msec (two-sided 90% Upper CI: 17.2) respectively. QTcF of >500 msec was observed in 4 (1.2%) of CML-CP patients. QTcF > 60 msec increase from baseline was observed in the combined CML-CP and -AP patient populations (CML-CP 8 (2.5%) and CML-AP 11 (8%).

In a healthy volunteer study (A2119), peak plasma concentrations were 26% lower than in the clinical study in CML patients. The maximum mean placebo-adjusted QTcF increase from baseline was 18 msec (1 -sided 95% Upper CI: 26 msec). In addition, no clinically relevant arrhythmias were observed during the conduct of the trial. In particular, no episodes of Torsades de Pointes (either transient or sustained) were observed.

Clinically meaningful 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, concomitant administration should be avoided (see **Drug-Food Interactions** and **Drug-Drug Interactions**).

The presence of hypokalemia and hypomagnesemia may place patients at risk of developing QT prolongation (see **DOSAGE AND ADMINISTRATION**).

TASIGNA should be avoided in patients who are at significant risk of developing prolongation of QTc interval, such as: patients taking anti-arrhythmic medicines or other drugs that may lead to QT prolongation, and cumulative high-dose anthracycline therapy. Hypokalemia or hypomagnesemia must be corrected prior to TASIGNA administration (See **Drug-Drug Interactions** and **DOSAGE AND ADMINISTRATION**).

TASIGNA should be used with caution in patients with uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure (CHF), unstable angina or clinically significant bradycardia.

### **Cardiovascular**

In clinical studies, newly diagnosed Ph+ CML-CP and imatinib-resistant or -intolerant Ph+ CML-CP and CML-AP patients with any of the following uncontrolled or significant cardiac disease were excluded: recent myocardial infarction, CHF, unstable angina, or clinically significant bradycardia. Imatinib-resistant or -intolerant Ph+ CML-CP and CML-AP patients with complete left bundle branch block and/or right bundle branch block, with left anterior hemiblock, or with bifascicular block were excluded from the study. Newly diagnosed Ph+ CML-CP patients with complete left bundle branch block were also excluded. ECG and cardiac enzyme monitoring were conducted in patients throughout the studies.

In newly diagnosed Ph+ CML-CP, left ventricular ejection fraction (LVEF) was assessed by echocardiography at baseline (within 14 days prior to the initial dose of nilotinib) in all patients. LVEF assessment was repeated in these patients on a regular basis and as clinically indicated thereafter. No patients in any treatment groups had a LVEF <45% during treatment. Also, there were no patients with 15% or greater decrease from baseline in LVEF.

In imatinib-resistant or -intolerant Ph+ CML-CP and CML-AP patients, LVEF was assessed by echocardiography or MUGA scan at baseline (within 14 days prior to the initial dose of nilotinib) in 49/438 patients. LVEF assessment was repeated in these patients as clinically indicated thereafter, and at the time of study completion. There was no clinically significant change in LVEF from baseline in the assessed patients.

Cardiovascular adverse reactions have been observed in patients in the TASIGNA clinical studies at the recommended doses including cardiac failure observed in <1% of patients in imatinib-resistant or -intolerant Ph+ CML-CP and CML-AP patients, and in newly diagnosed Ph+ CML-CP patients. In a Phase III study (A2303) in newly diagnosed Ph+ CML patients, with a median time on therapy of 60.5 months in the clinical trial, cases of cardiovascular events included ischemic heart disease-related events (5.0% and 9.4% in the nilotinib 300 mg and 400 mg twice daily groups respectively, and 2.5% in the imatinib arm), peripheral arterial occlusive disease (3.6% and 2.9% in the nilotinib 300 mg and 400 mg twice daily groups respectively, and 0% in the imatinib arm), and ischemic cerebrovascular events (1.4% and 3.2% in the nilotinib 300 mg and 400 mg twice daily groups respectively, and 0.7% in the imatinib arm).

Peripheral arterial occlusive disease, ischemic heart disease and ischemic cerebrovascular events include events such as femoral artery stenosis, coronary artery stenosis, cerebrovascular accident, vascular graft occlusion, arterial stenosis limb and carotid artery stenosis. Peripheral arterial occlusive disease can be severe, rapidly evolving and may affect more than one site. Peripheral arterial occlusive disease might require repeated revascularization procedures and can result in complications that may be serious such as limb necrosis and amputations. Most of the patients who developed cardiovascular adverse reactions had pre-existing documented cardiovascular disease or risk factors for atherosclerotic-related disease.

Of the 365 patients treated with TASIGNA, who had no documented pre-existing risk factors for cardiovascular disease, 19 patients (5%) experienced atherosclerotic-related events. Since it is not known whether TASIGNA caused or exacerbated these conditions, patients should be monitored during treatment with TASIGNA for signs of atherosclerotic-related conditions and actively managed during TASIGNA therapy according to standard guidelines. If acute signs or symptoms of cardiovascular events occur, advise patients to seek immediate medical attention. Administer with caution in patients with pre-existing risk factors for atherosclerosis (See **Monitoring and Laboratory Tests, DOSAGE AND ADMINISTRATION/Non-hematological toxicities, ADVERSE REACTIONS and Post-Market Adverse Reactions**).

### **Hemorrhage**

Gastrointestinal and CNS hemorrhage were reported in 1% and <1% of imatinib-resistant or -intolerant Ph+ CML-CP and CML-AP patients, respectively. In newly diagnosed Ph+ CML-CP, gastrointestinal hemorrhage, regardless of causality, was reported in 3% in the patients receiving TASIGNA 300 mg twice daily and in 5% in the patients receiving TASIGNA 400 mg twice daily. CNS hemorrhage, regardless of causality, was reported in <1% of the newly diagnosed Ph+ CML-CP patients receiving TASIGNA 300 mg and in patients receiving TASIGNA 400 mg twice daily (See **ADVERSE REACTIONS**).

### **Hematologic**

#### **Myelosuppression**

Treatment with TASIGNA is often associated with thrombocytopenia, neutropenia and anemia (NCI CTC Grade 3/4). The occurrence is more frequent in patients with imatinib-resistant or -intolerant CML and in particular in patients with CML-AP. 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 reducing the dose (see **DOSAGE AND ADMINISTRATION**).

### **Hepatic/Biliary and Pancreatic**

**Hepatotoxicity/Hyperbilirubinemia:** TASIGNA may result in elevation of bilirubin due to competitive inhibition of Uridine-Diphosphate-Glucuronyl Transferase (UGT1A1) and in elevation of AST, ALT and alkaline phosphatase (see **Drug-Drug Interactions and ADVERSE REACTIONS**). Patients taking TASIGNA who may be predisposed to or who may have

Gilbert's syndrome may have a higher risk of unconjugated hyperbilirubinemia. This may also occur in patients who are taking drugs known to inhibit UGT1A1.

**Hepatic Failure:** Twenty five cases of hepatic failure were reported in CML patients. Five of these were fatal including one case with no previous hepatic impairment. There were 29 cases of ascites reported in pooled clinical trials data which included all adverse events regardless of causality and the patient population. Three cases of hepatic steatosis and 2 cases of hepatic necrosis were reported in all clinical trial patients (see **DOSAGE AND ADMINISTRATION**). One of those fatal cases which satisfied Hy's Law was hepato-renal syndrome and fulminant hepatitis reported in a 23 year old male CML patient who had received 4 months of treatment with TASIGNA. Two cases of cytolytic hepatitis were reported in newly diagnosed Ph+ CML-CP patients.

**Elevated Serum Lipase/Amylase:** Grade 3/4 elevation in serum lipase and amylase have been observed. Few of these elevations were associated with abdominal pain or pancreatitis. There were 5 cases (1.1%) of pancreatitis reported in imatinib-resistant or -intolerant Ph+ CML-CP and CML-AP patients (N= 458). In newly diagnosed Ph+ CML-CP, 5 (1.8%) and 8 (2.9%) cases of pancreatitis were reported in patients receiving TASIGNA 300 mg twice daily (N=279), and 400 mg twice daily (N=277) respectively. Caution is recommended in patients with previous history of pancreatitis. In case lipase elevations are accompanied by abdominal symptoms, doses should be interrupted and appropriate diagnostics should be considered in order to rule out pancreatitis (see **DOSAGE AND ADMINISTRATION**).

### **Endocrine and Metabolism**

New-onset diabetes/hyperglycemia were reported with a common frequency (4.8%) in CML patients in completed clinical trials. In addition cases of exacerbated diabetes have been reported from post-marketing experience (see **ADVERSE REACTIONS**).

### **Fluid Retention**

Medically severe forms of drug-related fluid retention such as Grade 3 or 4 pleural effusion, pulmonary edema, and pericardial effusion were reported with an uncommon frequency (0.1 to 1%) observed in a Phase III study of newly diagnosed Ph+ CML-CP patients. Similar events were observed in post-marketing reports. Unexpected, rapid weight gain should be carefully investigated. If signs or symptoms of severe fluid retention appear during treatment with TASIGNA, the etiology should be evaluated and patients treated accordingly (see **Monitoring and Laboratory Tests, DOSAGE AND ADMINISTRATION/Non-hematological toxicities, Drug-Drug Interactions**).

### **Renal**

Acute renal failure (including a fatality) has been reported in 4 CML patients (uncommon frequency).

### **Respiratory**

Four cases of interstitial lung disease (Grade 3/4) have been reported (uncommon frequency) in CML patients.



### **Tumour Lysis Syndrome**

Cases of tumor lysis syndrome have been reported in patients treated with TASIGNA in pooled clinical trials. For monitoring recommendations (see **DOSAGE AND ADMINISTRATION**).

### **Immune**

Six cases of vasculitis (including 1 cerebral) have been reported in pooled clinical trials data which included all adverse events regardless of causality and the patient population (see **ADVERSE REACTIONS**).

### **Hepatitis B virus reactivation**

Reactivation of hepatitis B virus (HBV) has occurred in patients who are chronic carriers of this virus after receiving a BCR-ABL tyrosine kinase inhibitor (TKI), including TASIGNA. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or death.

Patients should be tested for HBV infection before initiating treatment with TASIGNA. Patients currently on TASIGNA should have baseline testing for HBV infection in order to identify chronic carriers of the virus. Experts in liver disease and in the treatment of hepatitis B should be consulted before treatment is initiated in patients with positive HBV serology (including those with active disease) and for patients who test positive for HBV infection during treatment. Carriers of HBV who require treatment with TASIGNA should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy.

### **Musculoskeletal**

Several cases of possible rhabdomyolysis, and some with concomitant elevations in serum creatinine, creatine kinase, creatine phosphokinase and hepatic transaminases, have been reported (unknown frequency). Several of these cases had pre-existing risk factors and/or were receiving concomitant medications known to be associated with this adverse event (see **ADVERSE REACTIONS**).

### **Sexual Function/Reproduction**

#### **Fertility**

The effect of TASIGNA on male and female fertility in humans is not known. Increased post-implantation loss was observed in both the fertility study, with the treatment of both female and male rats, and in the embryotoxicity study with the treatment of female rabbits (see **TOXICOLOGY, Reproductive toxicity studies**). Sexually active male or female patients taking TASIGNA should use highly effective contraception. Prior to initiating TASIGNA therapy, physicians should advise and counsel their patients as appropriate (see **WARNINGS AND PRECAUTIONS, Females of childbearing potential and Male patients**).

## **Carcinogenesis and Mutagenesis**

In the 2-year rat carcinogenicity study conducted orally at TASIGNA at 5, 15, and 40 mg/kg/day, there was a non-statistically significant increased incidence of uterine hemangiosarcoma, adenocarcinoma and squamous cell carcinoma and an increase in follicular cell adenoma in the thyroid gland (barely reaching statistical significance). Given that the incidence of thyroid follicular cell adenoma and uterine adenocarcinoma were within the historical control range, the data do not clearly indicate that TASIGNA is carcinogenic in rats. Exposures (in terms of AUC) at the highest dose level represented approximately 2x to 3x human daily steady state exposure at the dose of 800 mg/day. TASIGNA is not mutagenic (see **TOXICOLOGY**).

In the 26-week Tg.rasH2 mouse carcinogenicity study, in which nilotinib was administered at 30, 100 and 300 mg/kg/day, skin papillomas/carcinomas were detected at 300 mg/kg, representing approximately 30 to 40 times (based on AUC) the human exposure at the maximum approved dose of 800 mg/day (administered as 400 mg twice daily). The No-Observed-Effect-Level for the skin neoplastic lesions was 100 mg/kg/day, representing approximately 10 to 20 times the human exposure at the maximum approved dose of 800 mg/day (administered as 400 mg twice daily).

The relevance of the findings from the rat and mouse carcinogenicity studies for humans is not known at this time.

## **Special Populations**

### **Renal Impairment**

Clinical studies have not been performed in patients with impaired renal function. Clinical studies have excluded patients with serum creatinine concentration >1.5 times the upper limit of the normal range.

TASIGNA and its metabolites are not renally excreted (See **Pharmacokinetics**).

Due to the potential for tumour lysis syndrome in patients treated with TASIGNA, patients with decreased renal function may be at increased risk (See **MONITORING AND LABORATORY TESTS and DOSAGE AND ADMINISTRATION**).

### **Hepatic impairment**

Hepatic impairment has an effect on the pharmacokinetics of TASIGNA. Single dose administration of TASIGNA 200 mg resulted in increases in AUC of 35%, 35% and 56% in subjects with mild, moderate and severe hepatic impairment, respectively compared to a control group of subjects with normal hepatic function. The steady-state  $C_{max}$  of TASIGNA will likely to be increased by up to approximately 29% in subjects with hepatic impairment. Clinical studies have excluded patients with ALT and/ or AST >2.5 (or >5, if related to disease) times the upper limit of the normal range and/ or total bilirubin >1.5 times the upper limit of the normal range. Metabolism of nilotinib is mainly hepatic. TASIGNA should be used with caution and careful clinical monitoring (including close monitoring of the QTc interval) in patients with hepatic impairment (see **DOSAGE AND ADMINISTRATION**).

### *Gilbert's syndrome*

Due to a polymorphism in the enzyme UGT1A1 in patients who may be predisposed to Gilbert's syndrome, or in patients with Gilbert's syndrome, a higher risk unconjugated hyperbilirubinemia with nilotinib can occur, but is clinically benign and potentially persistent. No specific medical intervention is warranted (see **DOSAGE AND ADMINISTRATION**).

## **Peri-Operative Considerations**

### **Total gastrectomy**

The bioavailability of nilotinib was shown to be reduced in patients administered 400 mg bid TASIGNA with total gastrectomy versus non-gastrectomized patients (see **Pharmacokinetics** section).

### **Sensitivity/Intolerance**

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

### **Pregnant Women**

There are limited data on the use of TASIGNA in pregnant women. TASIGNA should not be used during pregnancy. There have been post-market reports of serious adverse events (spontaneous abortions, premature delivery, fetal abnormalities and/or deaths) from women who have taken TASIGNA during pregnancy (see **ADVERSE REACTIONS, Post Market Adverse Reactions, Pregnancy, Puerperium and Perinatal conditions, and Congenital, Familiar and Genetic Disorders**).

Studies in pregnant rats and rabbits showed maternal and embryo-fetal toxicity and lethality at exposures to nilotinib comparable to the human exposure (see **TOXICOLOGY, Reproductive toxicity studies**). Nilotinib and/or its metabolites showed placenta transfer to the fetus which may account for the incidence of embryo-lethal and embryotoxicity (see **DETAILED PHARMACOLOGY, Animal pharmacokinetics**).

Therefore, pregnant women must be informed of the potential harm to the fetus prior to initiation of TASIGNA therapy. If a patient becomes pregnant while taking TASIGNA, the benefits of therapy versus the potential risks of the fetus should be evaluated by the physician and the treatment options should be discussed with the patients.

### **Nursing Women**

It is unknown if nilotinib is excreted in human milk. Animal studies demonstrate that nilotinib is excreted into breast milk of rats (see **TOXICOLOGY, Animal pharmacokinetics**). Women taking TASIGNA should not breast-feed while taking TASIGNA, as a risk to the infant cannot be excluded.

### **Male Patients:**

It is not known if nilotinib is present in semen. Sexually active male patients must always use highly effective contraception during the treatment and for at least 4 weeks after ending TASIGNA therapy. There are post-market reports for pregnancies occurring in the female partners of male

patients who were receiving TASIGNA. Outcomes include spontaneous abortions, premature delivery and fetal abnormalities (see **ADVERSE REACTIONS, Post-Market Adverse Reactions**).

Therefore, male patients must be advised to inform their female sexual partners that they are taking TASIGNA. Male patients should also advise their female partners of the potential serious risks to a developing fetus should pregnancy occur during her partner's treatment with TASIGNA.

### **Females of Childbearing Potential**

Females of child-bearing potential are all females who are menstruating, or who are physiologically capable of becoming pregnant.

TASIGNA can cause fetal harm should pregnancy occur (See **WARNINGS AND PRECAUTIONS, Pregnant Women**). Female of childbearing potential must be advised to use highly effective method of contraception while receiving TASIGNA and at least 4 weeks after ending treatment. Highly effective contraception is a method of birth control which results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly. If a patient becomes pregnant while taking TASIGNA, the benefits of therapy versus the potential risks of the fetus should be evaluated by the physician and the treatment options should be discussed with the patients.

### **Pediatrics**

Safety and efficacy in children and adolescents below the age of 18 has not been established.

**Geriatrics (≥ 65 years of age):** Approximately 12% and 30% of subjects in the clinical studies (Phase III study (A2303) in newly diagnosed Ph+ CML-CP; and Phase II study (A2101) in resistant or -intolerant Ph+ CML-CP and CML-AP) were 65 years of age or older respectively. No major differences were observed for safety and efficacy in patients ≥65 years of age as compared to adults 18 to 65 years of age.

### **Monitoring and Laboratory Tests**

Complete blood counts should be performed every two weeks for the first 2 months and then monthly thereafter or as clinically indicated (See **WARNINGS AND PRECAUTIONS**).

Electrocardiograms (ECGs) should be obtained before treatment, seven days after initiation and periodically thereafter, as well as following dose adjustments (See **WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION**).

Liver function, (transaminases, total bilirubin and alkaline phosphatase) needs to be monitored before treatment, frequently during treatment, following dose adjustments or as clinically indicated (see **WARNINGS AND PRECAUTIONS; DOSAGE AND ADMINISTRATION; TOXICOLOGY**).

Serum electrolytes (including phosphorus) as well as serum lipase/amylase, fasting glucose, HbA1C, creatine kinase (CPK), uric acid, creatinine, and lactate dehydrogenase (LDH) levels

need to be monitored before treatment and frequently during treatment with TASIGNA and as clinically indicated (See **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**). Patients with symptomatic PAOD should be monitored and actively managed during TASIGNA therapy according to standard guidelines.

Adequate hydration should be maintained if tumor lysis syndrome is considered a substantial risk.

In a Phase III study in newly diagnosed CML patients, 1.1% of the patients treated with 400 mg TASIGNA twice a day, had a Grade 3/4 elevation in total serum cholesterol; however, there were no Grade 3/4 elevations in the group receiving the recommended dose of 300 mg twice a day (See **ADVERSE REACTIONS/Investigations**). It is recommended that the lipid profiles be determined before initiating treatment with TASIGNA, assessed at month 3 and 6 after initiating therapy, and at least yearly during therapy (See **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION/ Dose Adjustments or Modifications**). If test results warrant therapy, physicians should follow their local standards of practice and treatment guidelines. If lipid lowering agents are needed, please refer to **Drug-Drug Interactions section** before starting treatment.

Patients should be weighed and monitored regularly for signs and symptoms of fluid retention (see **WARNINGS AND PRECAUTIONS**). If therapeutic measures include the use of medications, please refer to **Drug-Drug Interactions section** before starting treatment.

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

#### **Sudden Cardiac Deaths**

From clinical trials including the Phase II study (A2101), the Expanded Access Program, and the Compassionate Use Program, 19 cases of sudden cardiac deaths have been reported out of 11,351 patients receiving TASIGNA (uncommon frequency of 0.17%). Of the 19 cases, 13 documented cases had a past medical history of cardiac disease or significant cardiac risk factors for sudden cardiac death. In 4 of the 19 cases of sudden cardiac death, patients had no prior medical history of cardiac disease. Comorbidities in addition to the underlying malignancy were also frequently present as were concomitant medications. Ventricular repolarization abnormalities may have been contributory factors. No cases of sudden cardiac deaths have been reported in any treatment group in the newly diagnosed Ph+ CML-CP Phase III study.

#### **Clinical Trial Adverse Drug Reactions**

## Summary of the safety profile

The TASIGNA safety profile is based on data from patients with newly diagnosed Ph+ CML-CP in a randomized, open label, active comparator-controlled Phase-III trial and patients with resistant or intolerant Ph+ CML-CP and CML-AP which served as a basis for the market authorized indications (see **Table 1** and **INDICATIONS AND CLINICAL USE**).

### In patients with newly diagnosed Ph+ CML-CP

The data reported below reflect exposure to TASIGNA from a randomized Phase III study (A2303) in patients with newly diagnosed Ph+ CML in chronic phase (CP) treated at the recommended dose of TASIGNA 300 mg twice daily (N=279), with a median time on treatment of 60.5 months (range 0.1 – 70.8 months). Among the patients with newly diagnosed Ph+ CML-CP treated with TASIGNA at 400 mg twice daily (N=277), the median time on treatment was 60.7 months (range 0.2 – 71.8 months).

The very common ( $\geq 10\%$ ) non-hematologic adverse drug reactions (ADRs) were rash, pruritus, headache, nausea, alopecia, myalgia, and fatigue in the TASIGNA 300 mg twice daily group and 400 mg twice daily group. Most of these ADRs were mild to moderate in severity (Grade 1 or 2). Upper abdominal pain was very frequent in the 300 mg twice daily group and less frequent in the 400 mg twice daily group, whereas arthralgia and dry skin were very frequent in the 400 mg twice daily group and less frequent in the 300 mg twice daily group.

Diarrhea, constipation, muscle spasms, vomiting, abdominal pain, peripheral oedema, dyspepsia, and asthenia were less frequent ( $< 10\%$  and  $\geq 5\%$ ) in the TASIGNA 300 mg twice daily group and 400 mg twice daily group. They were mild to moderate severity, manageable and generally did not require dose reduction. In addition, erythema, and bone pain were less frequent ( $< 10\%$  and  $\geq 5\%$ ) in the 300 mg twice daily group whereas pain in the extremity was observed less frequently ( $< 10\%$  and  $\geq 5\%$ ) in the 400 mg twice daily group.

Pleural and pericardial effusions occurred in  $< 1\%$  of patients, receiving TASIGNA 300 mg twice daily and TASIGNA 400 mg twice daily. Grade 3 or 4 pleural effusion occurred in a patient receiving TASIGNA 300 mg twice daily.

Gastrointestinal hemorrhage, regardless of causality, was reported in 3% in patients receiving TASIGNA 300 mg twice daily and in 5% patients receiving TASIGNA 400 mg twice daily.

The maximum QTcF mean increase from baseline in the TASIGNA 300 mg twice daily group was 12.3-msec (two-sided 90% Upper CI: 14.4) and the maximum QTcF mean increase from baseline in the TASIGNA 400 mg twice daily group was 12.9-msec (two-sided 90% Upper CI: 15.1).

No patient had an absolute QTcF of  $> 500$  msec while on treatment drug in any of the TASIGNA treatment groups and no events of Torsades de Pointes were observed. One patient in the 400 mg twice daily arm had an absolute QTcF of  $> 480$  msec. QTcF increase from baseline that exceeds 60 msec was observed in 5 patients while on TASIGNA (one in the TASIGNA 300 mg twice daily treatment group and four in the TASIGNA 400 mg twice daily treatment group). No patients in any treatment group had a LVEF  $< 45\%$  during treatment. Also, there were no patients with 15% or greater decrease from baseline in LVEF.

No sudden cardiac deaths have been reported in any treatment group.

Hematologic ADRs include myelosuppression in patients receiving TASIGNA 300 mg twice daily and 400 mg twice daily respectively: thrombocytopenia (18%; 20%), neutropenia (15%; 11%), and anemia (8%; 9%). Biochemistry ADRs in patients receiving TASIGNA 300 mg twice daily and 400 mg twice daily, respectively include: alanine aminotransferase increased (24%; 29%), hyperbilirubinemia (17%; 17%), aspartate aminotransferase increased (12%; 15%), lipase increased (11%; 10%), blood bilirubin increased (10%; 14%), hyperglycemia (4%; 5%), hypercholesterolemia (3%; 6%), and hypertriglyceridemia (<1%; 1%). See **Table 2** for Grade 3/4 laboratory abnormalities.

Discontinuation due to adverse drug reactions was observed in 10% of patients receiving TASIGNA 300 mg twice daily and in 17% of patients receiving TASIGNA 400 mg twice daily.

### **In patients with resistant or intolerant Ph+ CML-CP and CML-AP**

The data reported below reflect exposure to TASIGNA in 458 patients with Ph+ CML-CP and CML-AP resistant to or intolerant to at least one prior therapy including imatinib (321 CML-CP patients and 137 CML-AP patients, respectively) in an open-label multicenter study. Patients were treated at the recommended dose of 400 mg twice daily.

Non-hematologic adverse drug reactions (ADRs) reported with very common frequency ( $\geq 10\%$  in the combined CML-CP and CML-AP patient populations) were rash, pruritus, nausea, fatigue, headache, constipation and diarrhea, vomiting and myalgia. Most of these ADRs were mild to moderate in severity. Alopecia, muscle spasms, decreased appetite, arthralgia, bone pain, abdominal pain, peripheral oedema and asthenia were observed less frequently (<10% and  $\geq 5\%$ ) and have been of mild to moderate severity (Grade 1 or 2).

Pleural and pericardial effusions as well as complications of fluid retention occurred in <1% of patients receiving TASIGNA.

Cardiac failure was observed in <1% of patients. QTcF exceeding 500 msec was observed in this study in 4 patients (< 1%). No episodes of Torsades de Pointes (transient or sustained) were observed.

Gastrointestinal and CNS hemorrhage was reported in 1% and <1% of patients, respectively.

Hematologic ADRs include myelosuppression: thrombocytopenia (31%), neutropenia (17%), and anemia (14%). See Table 2 for Grade 3/4 laboratory abnormalities.

Discontinuation due to adverse drug reactions was observed in 16% of CP and 10% of AP patients.

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

Non-hematologic ADRs (excluding laboratory abnormalities) that were reported in at least 5% of the patients in any of the TASIGNA clinical studies are shown in Table 1. These are ranked under heading of frequency, the most frequent first. Within each frequency grouping adverse drug reactions are presented in order of decreasing seriousness. In addition the corresponding frequency category for each adverse drug reaction is based on the following convention: very common ( $\geq 10\%$ ) or common ( $\geq 1\%$  to < 10%). The frequency is based on the highest for any TASIGNA group in the two studies, using one decimal precision for percentages.

**Table 1 Most Frequently Reported Non-hematologic Adverse Drug Reactions (≥ 5% in any TASIGNA Group)**

Newly Diagnosed Ph+ CML-CP 60 month analysis								Resistant or Intolerant Ph+ CML-CP and CML-AP 24-month analysis			
		TASIGNA 300 mg twice daily	TASIGNA 400 mg twice daily	GLEEVEC® 400 mg once daily	TASIGNA 300 mg twice daily	TASIGNA 400 mg twice daily	GLEEVEC® 400 mg once daily	TASIGNA 400 mg twice daily			
		ALL Grades (%)			Grade 3/4 (%)			ALL Grades (%)	Grade 3/4 (%)	CML-CP Grade 3/4 (%)	CML- AP Grade 3/4 (%)
System Organ Class	Adverse Reaction	N=279 %	N=277 %	N=280 %	N=279 %	N=277 %	N=280 %	N=458 %	N=458 %	N=321 %	N=137 %
Metabolism and nutrition disorders	Decreased appetite <sup>1</sup>	4	4	3	0	0	0	8	<1	<1	0
Nervous system disorders	Headache	16	22	10	2	1	<1	15	1	2	<1
Gastrointestinal disorders	Nausea	14	21	35	<1	1	<1	20	<1	<1	<1
	Constipation	10	7	3	0	<1	0	12	<1	<1	0
	Diarrhea	9	7	31	<1	0	3	11	2	2	<1
	Vomiting	6	9	19	0	1	0	10	<1	<1	0
	Abdominal pain upper	10	9	8	1	0	<1	5	<1	<1	0
	Abdominal pain	6	6	4	0	<1	0	6	<1	<1	<1
Skin and subcutaneous tissue disorders	Dyspepsia	5	5	6	0	<1	0	3	0	0	0
	Rash	33	39	14	<1	3	2	28	1	2	0
	Pruritus	18	16	5	<1	<1	0	24	<1	<1	0
	Alopecia	10	14	6	0	0	0	9	0	0	0



	Dry Skin	10	12	5	0	0	0	5	0	0	0
	Erythema	3	6	3	0	0	0	5	<1	<1	0
<b>Musculoskeletal and connective tissue disorders</b>	Myalgia	10	12	13	<1	<1	<1	10	<1	<1	<1
	Arthralgia	8	10	8	<1	0	<1	7	<1	1	0
	Muscle spasms	9	9	30	0	<1	1	8	<1	<1	0
	Bone pain	4	5	4	0	<1	<1	6	<1	<1	0
	Pain in extremity	5	3	8	<1	<1	<1	5	<1	<1	<1
<b>General disorders and administration site conditions</b>	Fatigue	12	11	13	0	<1	1	17	1	1	<1
	Asthenia	9	5	9	<1	<1	0	6	0	0	0
	Oedema peripheral	5	7	18	<1	0	0	6	0	0	0

<sup>1</sup> Also includes preferred term anorexia

Percentages are rounded to integer for presentation in this table. However, percentages with one decimal precision are used to identify terms with a frequency of at least 5% and to classify terms according to frequency categories

## **Common Clinical Trial Adverse Drug Reactions (< 5%)**

### **Additional Data from Clinical Trials (Studies A2101 and A2303)**

The following adverse drug reactions (ADRs) were reported in patients in the TASIGNA clinical studies at the recommended doses at a frequency of less than 5% (common is  $\geq 1\%$  to  $< 10\%$ ; uncommon is  $>0.1\%$  to  $<1\%$ ); (single events are captured as Unknown in *frequency- Unknown*). For laboratory abnormalities, very common events ( $\geq 10\%$ ) not included in Table 1 are also reported. These adverse reactions are included based on clinical relevance and ranked in order of decreasing seriousness within each category, obtained from two clinical studies: 1. Newly diagnosed Ph+ CML-CP 60 months' analysis and 2. Resistant or intolerant Ph+ CML-CP and CML-AP 24 months' analysis.

#### **Cardiac Disorders:**

*Common:* angina pectoris, arrhythmia (including atrioventricular block, cardiac flutter, extrasystoles, atrial fibrillation, tachycardia, bradycardia), cardiac failure, palpitations, electrocardiogram QT prolonged.

*Uncommon:* myocardial infarction, coronary artery disease, cardiac murmur pericardial effusion, deep vein thrombosis, cyanosis

*Unknown frequency:* myocarditis, ventricular dysfunction, pericarditis, ejection fraction decrease, congenital transposition of great vessels in neonate (fatal), ventricular arrhythmia, cardiac valve disorders

#### **Infections and Infestations:**

*Common:* folliculitis, upper respiratory tract infection (including pharyngitis, nasopharyngitis, rhinitis).

*Uncommon:* pneumonia, bronchitis, urinary tract infection, herpes virus infection, candidiasis (including oral candidiasis), gastroenteritis

*Unknown frequency:* sepsis, subcutaneous abscess, anal abscess, furuncle, tinea pedis, hepatitis B virus reactivation.

#### **Neoplasms Benign, Malignant and Unspecified:**

*Common:* skin papilloma.

*Unknown frequency:* oral papilloma, paraproteinemia.

#### **Blood and Lymphatic System Disorders:**

*Common:* leukopenia, eosinophilia, febrile neutropenia, pancytopenia, lymphopenia.

*Unknown frequency:* thrombocythemia, leukocytosis.

#### **Endocrine Disorders:**

*Uncommon:* hyperthyroidism, hypothyroidism.

*Unknown frequency:* hyperparathyroidism secondary, thyroiditis.

#### **Metabolism and Nutrition Disorders:**

*Very Common:* hypophosphatemia (including blood phosphorus decreased).

*Common:* electrolyte imbalance (including hypomagnesemia, hyperkalemia, hypokalemia, hyponatremia, hypocalcemia, hypercalcemia, hyperphosphatemia), diabetes mellitus

(uncommonly specified as Types 1 or 2 diabetes mellitus), hyperglycemia, hypercholesterolemia, hypertriglyceridemia, hyperlipidemia.

*Uncommon:* gout, dehydration, increased appetite, new-onset diabetes, dyslipidemia

*Unknown frequency:* hyperuricemia, hypoglycemia.

### **Psychiatric Disorders:**

*Common:* depression, insomnia, anxiety.

*Unknown frequency:* disorientation, confusional state, amnesia, dysphoria.

### **Nervous System Disorders:**

*Common:* dizziness, peripheral neuropathy, hypoaesthesia, paresthesia.

*Uncommon:* intracranial hemorrhage, ischemic stroke, transient ischemic attack, cerebral infarction, migraine, loss of consciousness (including syncope), tremor, disturbance in attention, hyperesthesia.

*Unknown frequency:* cerebrovascular accident, basilar artery stenosis, brain oedema, optic neuritis, lethargy, dysaesthesia, restless legs syndrome.

### **Eye Disorders:**

*Common:* eye hemorrhage, periorbital oedema, eye pruritus, conjunctivitis, dry eye (including xerophthalmia).

*Uncommon:* vision impairment, vision blurred, visual acuity reduced, eyelid oedema, photopsia, hyperaemia (scleral, conjunctival, ocular), eye irritation, conjunctival hemorrhage.

*Unknown frequency:* papilloedema, diplopia, photophobia, eye swelling, blepharitis, eye pain, chorioretinopathy, conjunctivitis allergic, ocular surface disease.

### **Ear and Labyrinth Disorders:**

*Common:* vertigo.

*Unknown frequency:* hearing impaired, ear pain, tinnitus.

### **Immune System Disorders:**

*Unknown frequency:* vasculitis (cerebral, leukocytoclastic), hypersensitivity.

### **Vascular Disorders:**

*Common:* hypertension, flushing.

*Uncommon:* hypertensive crisis, peripheral arterial occlusive disease (including femoral artery stenosis), coronary artery stenosis, carotid artery stenosis, arterial stenosis limb, cerebrovascular accident, hematoma, arteriosclerosis.

*Unknown frequency:* shock hemorrhagic, arteriosclerosis obliterans, hypotension, thrombosis, cerebral infarction, cerebral hemorrhage, amnesic disorder, peripheral vascular disorder, intermittent claudication, vasculitis, circulatory collapse, venous stenosis, arterial disorder, femoral artery occlusion, aortic arteriosclerosis, peripheral ischaemia, arterial occlusive disease, arteritis obliterans, extravasation blood, vascular graft occlusion, peripheral artery stenosis.

### **Respiratory, Thoracic and Mediastinal Disorders:**

*Common:* dyspnea, dyspnea exertional, epistaxis, cough, dysphonia.

*Uncommon:* pulmonary oedema, pleural effusion, interstitial lung disease, pleuritic pain, pleurisy, pharyngolaryngeal pain, throat irritation.

*Unknown frequency:* pulmonary hypertension, wheezing, oropharyngeal pain.

### **Gastrointestinal Disorders:**

*Common:* acute pancreatitis, abdominal discomfort, abdominal distension, dyspepsia, dysgeusia, flatulence.

*Uncommon:* gastrointestinal hemorrhage, melaena, mouth ulceration, gastroesophageal reflux, stomatitis, oesophageal pain, dry mouth, gastritis, sensitivity of teeth.

*Unknown frequency:* gastrointestinal ulcer perforation, retroperitoneal hemorrhage, hematemesis, gastric ulcer, esophagitis ulcerative, subileus, enterocolitis, hemorrhoids, hiatus hernia, rectal hemorrhage, gingivitis.

### **Hepatobiliary Disorders:**

*Very common:* hyperbilirubinemia (including blood bilirubin increased).

*Common:* hepatic function abnormal.

*Uncommon:* hepatic failure, hepatotoxicity, toxic hepatitis, ascites, jaundice.

*Unknown frequency:* cholestasis, hepatic necrosis, hepatic steatosis, hepatomegaly.

### **Skin and Subcutaneous Tissue Disorders:**

*Common:* night sweats, eczema, urticaria, hyperhidrosis, contusion, acne, dermatitis, (including allergic, exfoliative and acneiform).

*Uncommon:* exfoliative rash, drug eruption, pain of skin, ecchymosis, swelling face.

*Unknown frequency:* psoriasis, erythema multiforme, skin fissures, erythema nodosum, skin ulcer, palmar-plantar erythrodysesthesia syndrome, petechiae, photosensitivity, blister, dermal cyst, sebaceous hyperplasia, skin atrophy, skin discoloration, skin exfoliation, skin hyperpigmentation, skin hypertrophy, hyperkeratosis.

### **Musculoskeletal and Connective Tissue Disorders:**

*Common:* musculoskeletal chest pain, musculoskeletal pain, back pain, neck pain, flank pain, muscular weakness.

*Uncommon:* musculoskeletal stiffness, joint swelling.

*Unknown frequency:* rhabdomyolysis, arthritis.

### **Renal and Urinary Disorders:**

*Common:* pollakiuria.

*Uncommon:* dysuria, micturition urgency, nocturia, acute renal failure.

*Unknown frequency:* renal failure, hematuria, urinary incontinence, chromaturia.

### **Reproductive System and Breast Disorders:**

*Uncommon:* breast pain, gynecomastia, erectile dysfunction.

*Unknown frequency:* breast induration, menorrhagia, nipple swelling.

### **General Disorders and Administration Site Conditions:**

*Common:* pyrexia, chest pain (including non-cardiac chest pain), pain chest discomfort, malaise.

*Uncommon:* face edema, gravitational edema, influenza-like illness, chills, feeling body temperature change (including feeling hot, feeling cold).

*Unknown frequency:* localised oedema.

**Investigations:**

*Very Common:* alanine aminotransferase increased, aspartate aminotransferase increased, lipase increased, lipoprotein cholesterol (including low density and high density) increased, total cholesterol increased, blood triglycerides increased.

*Common:* prothrombin time (INR) increased<sup>1</sup>, hemoglobin decreased, blood amylase increased, gamma-glutamyltransferase increased, blood creatine phosphokinase increased, blood alkaline phosphatase increased, weight decreased, blood insulin increased, weight increased, globulins decreased.

*Uncommon:* blood lactate dehydrogenase increased, blood urea increased.

*Unknown frequency:* troponin increased, blood potassium decreased, blood bilirubin unconjugated increased, blood insulin decreased, insulin C-peptide decreased, blood parathyroid hormone increased.

<sup>1</sup> Prolongation of prothrombin time (INR) was reported with common frequency in patients receiving TASIGNA, however causal relationship with TASIGNA has not been confirmed.

**Second malignancies in TASIGNA-treated patients:**

There are reports of second cancers (gastric cancer, gastrointestinal stromal tumour, pancreatic carcinoma, pancreatic neuroendocrine tumour, colon cancer, malignant melanoma in situ, ovarian epithelial cancer, skin cancer, and squamous cell carcinoma) in pooled clinical trials of patients treated with TASIGNA.

## Abnormal Hematologic and Clinical Chemistry Findings

Clinically relevant or severe abnormalities of routine hematologic or biochemistry laboratory values are presented in Table 2.

**Table 2            Grade 3/4 Laboratory Abnormalities**

	Newly diagnosed Ph+ CML-CP			Resistant or intolerant Ph+	
				CML-CP	CML-AP
	TASIGNA 300 mg twice daily N = 279	TASIGNA 400 mg twice daily N = 277	GLEEVEC 400 mg once daily N = 280	TASIGNA 400 mg twice daily N=321	TASIGNA 400 mg twice daily N=137
<b>Hematologic Parameters</b>					
Myelosuppression					
Neutropenia	12%	11%	22%	31%	42%
Thrombocytopenia	10%	12%	9%	30%	42%
Anemia	4%	5%	6%	11%	27%
<b>Biochemistry Parameters</b>					
Elevated creatinine	0%	0%	<1%	1%	<1%
Elevated lipase	9%	10%	4%	18%	18%
Elevated SGOT (AST)	1%	3%	1%	3%	2%
Elevated SGPT (ALT)	4%	9%	3%	4%	4%
Hypophosphatemia	8%	10%	10%	17%	15%
Elevated Bilirubin (total)	4%	9%	<1%	7%	9%
Hyperglycemia	7%	7%	<1%	12%	6%
Hyperkalemia	2%	1%	1%	6%	4%
Hyponatremia	1%	1%	<1%	7%	7%
Hypokalemia	<1%	1%	2%	2%	9%
Hypocalcemia	<1%	<1%	<1%	2%	5%
Decreased albumin	0%	0%	<1%	4%	3%
Elevated alkaline phosphatase	0%	0%	<1%	<1%	1%
Elevated cholesterol (total)	0	1%	0%	**	**
Elevated triglycerides	0%	<1%	0%	**	**

Percentages with one decimal precision are used and rounded to integer for presentation in this table.

\* parameter not collected

### **Abnormal Electrocardiographic (ECG) Findings**

In the Phase III study (A2303) in newly diagnosed Ph+ CML-CP, no patient had an absolute QTcF exceeding 500 msec while on treatment in any of the treatment groups. QTcF increase from baseline that exceeds 60 msec was observed in 1 patient (0.4%) in the TASIGNA 300 mg twice daily treatment group and 4 (1.4%) in the TASIGNA 400 mg twice daily treatment group (See Table 3). No episodes of Torsades de Pointes were observed.

In the Phase II study (A2101) in imatinib-resistant or -intolerant CML patients in CP and AP, QTcF exceeding 500 msec was observed in 4 patients (1.2%) of CML-CP patients. QTcF > 60 msec increase from baseline was observed in the combined CML-CP and -AP patient populations (CML-CP 8 (2.5%) and CML-AP 11 (8%) (See Table 4). No episodes of Torsades de Pointes (transient or sustained) were observed (see **WARNINGS AND PRECAUTIONS** and **ADVERSE REACTIONS**).

**Table 3 Number (%) of newly diagnosed Ph+ CML-CP patients with notable values in QTcF intervals-Study A2303**

<b>ECG Parameter</b>	<b>TASIGNA 300 mg twice daily N = 279 n (%)</b>	<b>TASIGNA 400 mg twice daily N = 277 n (%)</b>	<b>GLEEVEC 400 mg once daily N= 280 n (%)</b>
Increase from baseline > 30 msec	94 (33.7)	91 (32.9)	82 (29.3)
Increase from baseline > 60 msec	1 (0.4)	4 (1.4)	4 (1.4)
Absolute value > 450 msec	32 (11.5)	40 (14.4)	41 (14.6)
Absolute value > 480 msec	0	1 (0.4)	2 (0.7)
Absolute value > 500 msec	0	0	1 (0.4)

**Table 4 Number (%) of imatinib- resistant or -intolerant Ph+ CML-CP and CML-AP patients with notable values in QTcF intervals-Studies 2101E2 and 2101E1**

<b>ECG Parameter</b>	<b>CML-CP (2101E2) N= 321 n (%)</b>	<b>CML-AP (2101E1) N= 137 n (%)</b>	<b>Total N= 458 n (%)</b>
Increase from baseline > 30 msec	144 (44.9)	65 (47.4)	209 (45.6)
Increase from baseline > 60 msec	8 (2.5)	11 (8.0)	19 (4.1)
Absolute value > 450 msec	51(15.9)	24	75(16.4)

Absolute value > 480 msec	7 (2.2)	4 (2.9)	11(2.4)
Absolute value > 500 msec	4 (1.2)	0 (0.0)	4 (0.9)

n= number of patients who meet the criterion for at least one post-baseline value.

## Post-Market Adverse Reactions

The following adverse reactions have been derived from post marketing experience with TASIGNA via spontaneous case reports, literature cases, expanded access programs, and clinical studies other than the global registration trials. The criteria for including these adverse reactions is based on the seriousness. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**Blood and lymphatic :** splenic infarction

**Cardiovascular:** anaphylaxis, cardiac tamponade (fatal), Torsades de Pointes, tricuspid valve incompetence, aortic valve sclerosis, coeliac artery stenosis, disseminated intravascular coagulation

**Congenital, familial and genetic:** Encephalocele, omphalocele, transposition of great vessels, venous angioma of brain, cerebellar hypoplasia

**Ear and labyrinth:** deafness

**Endocrine and Metabolism:** fluid overload, tumor lysis syndrome

**Eye:** cataract, blindness, conjunctivitis, ocular hyperaemia, visual impairment, eye haemorrhage, periorbital oedema, retinal haemorrhage, optic nerve infarction, optic ischaemic neuropathy, arteriosclerotic retinopathy, optic neuropathy, retinal artery occlusion, optic neuritis

**General:** gait disturbance

**Hepatobiliary:** hepatorenal syndrome, diverticular perforation, intestinal perforation, gastric ulcer haemorrhage

**Immune:** aphthous stomatitis

**Infections and infestations:** Clostridium difficile colitis, lower respiratory tract infection, pelvic abscess, pneumonia primary atypical, septic shock, swine influenza

**Injury, poisoning and procedural complications:** In-stent arterial restenosis

**Investigations:** blood phosphorus increased, positive Rombergism, urine output decreased

**Neoplasms benign, malignant and unspecified (incl cysts and polyps):** biliary adenoma, biliary neoplasm, lung neoplasm malignant, renal cancer, transitional cell carcinoma, lymphoma, leukemia , myelodysplastic syndrome, skin papilloma, thyroid neoplasm, oesophageal adenocarcinoma, throat cancer, rhabdomyosarcoma, metastases to central nervous system, malignant lung neoplasm, bronchial carcinoma, acute lymphocytic leukemia, acute leukemia, squamous cell carcinoma of skin, malignant melanoma, penis carcinoma, carcinoid



tumour of small bowel, ovarian cancer, basal cell carcinoma, myelofibrosis, colon cancer, gastrointestinal stromal tumour

**Nervous system:** convulsion, hepatic encephalopathy, intracranial pressure increased, spinal cord infarction, paralysis, IIIrd nerve paralysis, Vth nerve paralysis, cerebellar infarction, brain herniation

**Pregnancy, puerperium and perinatal conditions:** Spontaneous abortions, stillbirth, and foetal death

**Psychiatric:** bipolar disorder, hallucination

**Renal and urinary:** calculus ureteric, tubulointerstitial nephritis, urine flow decreased

**Respiratory:** acute respiratory distress syndrome, acute respiratory failure, bronchospasm, hypoxia, pulmonary embolism, respiratory failure, tachypnoea

**Skin and subcutaneous:** Stevens-Johnson syndrome, skin necrosis, palmar-plantar erythrodysesthesia syndrome, exfoliative dermatitis, toxic epidermal necrolysis

**Vascular:** venous insufficiency, vertebral artery occlusion, cerebral artery stenosis, carotid artery thrombosis, carotid artery occlusion, cerebral artery occlusion, arterial occlusive disease, necrotising vasculitis, aortic stenosis, peripheral embolism, arterial haemorrhage, embolism venous, venous thrombosis, vascular occlusion, veno-occlusive disease

## **DRUG INTERACTIONS**

### **Overview**

### **Drug-Drug Interactions**

#### **Serious Drug and Drug-Food Interactions**

- CYP3A4 inhibitors should be avoided as they can increase nilotinib serum concentrations.
- Concomitant use of drugs that prolong QT interval should be avoided.
- Co-administration with drugs with a narrow therapeutic index and that are eliminated by certain enzymes.
- TASIGNA absorption is increased if taken with food. TASIGNA must not be taken with food and should be taken 2 hours after a meal. No food should be consumed at least 1 hour after the drug is taken.

Nilotinib is mainly metabolized in the liver, and is also a substrate for the multi-drug efflux pump, P-glycoprotein (P-gp). Therefore, absorption and subsequent elimination of systemically absorbed nilotinib may be influenced by drugs that affect CYP3A4 and/or P-gp.

### **Drugs That May Increase Nilotinib Serum Concentrations**

The administration of TASIGNA with agents that are strong CYP3A4 inhibitors should be avoided. Should treatment with any of these agents be required, it is recommended that therapy with TASIGNA be interrupted if possible. If transient interruption of treatment with TASIGNA is not possible, close monitoring of the individual for prolongation of the QT-interval is indicated (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY**).

In a Phase I study of nilotinib given in combination with imatinib (a substrate of P-gp and CYP3A4), both drugs had individually an inhibitory effect on CYP3A4 and/or P-gp. When the two drugs were administered concomitantly, the AUC of imatinib was increased by 18% to 39%, and the AUC of nilotinib was increased by 18% to 40%.

The bioavailability of nilotinib in healthy subjects was increased by 3-fold when co-administered with the strong CYP3A4 inhibitor **ketoconazole**. Concurrent treatment with strong CYP3A4 inhibitors should therefore be avoided (including but not limited to **ketoconazole, itraconazole, voriconazole, ritonavir, clarithromycin, and telithromycin**). For additional drugs, also refer to <http://www.intermed-rx.ca>. (see **DOSAGE AND ADMINISTRATION** and **WARNINGS AND PRECAUTIONS** regarding QT prolongation). Alternative concomitant medications with no or minimal CYP3A4 inhibition should be considered.

### **Drugs That May Decrease Nilotinib Serum Concentrations**

In healthy subjects receiving the CYP3A4 inducer, **rifampicin**, at 600 mg daily for 12 days, systemic exposure (AUC) to TASIGNA was decreased approximately 80%.

Inducers of CYP3A4 activity could increase the metabolism of nilotinib and thereby decrease plasma concentrations of nilotinib. The concomitant administration of medications that induce CYP3A4 (e.g. **phenytoin, rifampin carbamazepine, phenobarbital, and St. John's Wort**) may reduce exposure to nilotinib to a clinically relevant extent. In patients for whom CYP3A4 inducers are indicated, concomitant use of alternative therapeutic agents with less potential for CYP3A4 enzyme induction potential should be considered. For additional drugs, also refer to <http://www.intermed-rx.ca>.

Nilotinib has pH-dependent solubility, with lower solubility at higher pH. In 22 healthy subjects receiving multiple doses of esomeprazole at 40 mg once daily for 5 days, gastric pH was markedly increased. Co-administration of a single 400 mg dose of nilotinib and 40 mg esomeprazole was associated with a modest decrease in nilotinib absorption (27% decrease in nilotinib  $C_{max}$  and 34% decrease in nilotinib  $AUC_{0-\infty}$ ). TASIGNA may be used concurrently with esomeprazole or other proton pump inhibitors as needed.

In a study with 52 healthy subjects, no significant change in nilotinib pharmacokinetics was observed when a single 400 mg dose of TASIGNA was administered 10 hours after and 2 hours before famotidine. Therefore, when the concurrent use of an H2 blocker is necessary, it may be

administered approximately 10 hours before and approximately 2 hours after the dose of TASIGNA.

In the same study as above, administration of a “non-absorbable” antacid (aluminum hydroxide/magnesium hydroxide/simethicone) 2 hours before or after a single 400 mg dose of TASIGNA also did not alter nilotinib pharmacokinetics. Therefore, if necessary, a “non-absorbable” antacid may be administered approximately 2 hours before or approximately 2 hours after the dose of TASIGNA.

### **Drugs That May Have Their Systemic Concentration Altered By Nilotinib**

*In vitro* nilotinib is identified as a competitive inhibitor of CYP3A4, CYP2C8, CYP2C9, and CYP2D6 and UGT1A1, with  $K_i$  value being lowest for CYP2C9 ( $K_i=0.13 \mu\text{M}$ ) (Substrates of UGT1A1: including but not limited to **buprenorphine, phenytoin**). A single-dose drug-drug interaction study with 25 mg warfarin, a sensitive CYP2C9 substrate, and 800 mg nilotinib was conducted in 24 healthy subjects. Nilotinib at clinically relevant concentrations was not found to alter the pharmacokinetics or pharmacodynamics of warfarin, a sensitive CYP2C9 substrate. TASIGNA can be used concurrently with warfarin without increasing the anticoagulant effect. Due to lack of steady-state data, control of warfarin pharmacodynamic markers (INR or PT) following initiation of nilotinib therapy (at least during the first 2 weeks) is recommended.

In 19 CML patients, nilotinib administered at 400 mg twice daily for 12 days increased the systemic exposure (AUC) of a single 2 mg oral dose of midazolam (a substrate of CYP3A4) 2.6-fold. Nilotinib is a moderate CYP3A4 inhibitor. As a result, the systemic exposure of other drugs primarily metabolized by CYP3A4 (e.g. certain HMG-CoA reductase inhibitors or statins) may be increased when co-administered with nilotinib. Appropriate monitoring and dose adjustment may be necessary for drugs that are CYP3A4 substrates and have a narrow therapeutic index (including but not limited to opioids (alfentanil, fentanyl), immunosuppressants (cyclosporine, sirolimus and tacrolimus), vasoconstrictors (dihydroergotamine and ergotamine), and levothyroxine) when co-administered with nilotinib (see **Monitoring and Laboratory Tests**). For additional drugs, also refer to <http://www.intermed-rx.ca>.

Nilotinib is a P-gp inhibitor *in vitro*. Therefore, concentration of drugs which are substrates of P-gp (including but not limited to **verapamil, digoxin, morphine, phenytoin, cefazolin, cyclosporine A, ondansetron**) may be increased. Alternative concomitant medications which are not P-gp substrates should be considered.

### **Anti-arrhythmic Medicines and Other Drugs That May Prolong the QT Interval**

Concomitant use of TASIGNA with **anti-arrhythmic medicines** (including, but not limited to **amiodarone, disopyramide, procainamide, quinidine and sotalol**) and other drugs that may prolong the QT interval (including, but not limited to **chloroquine, halofantrine, clarithromycin, and other macrolides, haloperidol, methadone, moxifloxacin, bepridil and pimozide**) should be avoided. (see **WARNINGS AND PRECAUTIONS**).

Concomitant use of **anti-emetic medicines** (including but not limited to **metoclopramide, prochlorperazine, ondansetron and dolasetron**) should be avoided.

The concomitant use of TASIGNA with another QT/QTc-prolonging drug is discouraged. Drugs that have been associated with QT/QTc interval prolongation and/or Torsades de pointes include,

but are not limited to, the examples in the following list. Chemical/pharmacological classes are listed if some, although not necessarily all, class members have been implicated in QT/QTc prolongation and/or Torsades de pointes:

- Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide);
- Class III antiarrhythmics (e.g., amiodarone, sotalol, ibutilide);
- Class 1C antiarrhythmics (e.g., flecainide, propafenone);
- antipsychotics (e.g., chlorpromazine, pimozide, haloperidol, droperidol, ziprasidone);
- antidepressants (e.g., fluoxetine, citalopram, venlafaxine, tricyclic/tetracyclic antidepressants e.g., amitriptyline, imipramine, maprotiline);
- opioids (e.g., methadone);
- macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin, telithromycin, tacrolimus);
- quinolone antibiotics (e.g., moxifloxacin, levofloxacin, ciprofloxacin);
- pentamidine;
- antimalarials (e.g., quinine, chloroquine);
- azole antifungals (e.g., ketoconazole, fluconazole, voriconazole);
- domperidone;
- 5-hydroxytryptamine (5-HT)<sub>3</sub> receptor antagonists (e.g., dolasetron, ondansetron);
- tyrosine kinase inhibitors (e.g., sunitinib, lapatinib);
- histone deacetylase inhibitors (e.g., vorinostat);
- beta-2 adrenoceptor agonists (e.g., salmeterol, formoterol).

**The use of TASIGNA is discouraged with drugs that can disrupt electrolyte levels, including, but not limited to, the following:**

- loop, thiazide, and related diuretics;
- laxatives and enemas;
- amphotericin B;
- high dose corticosteroids.

*The above lists of potentially interacting drugs are not comprehensive. Current information sources should be consulted for newly approved drugs that prolong the QT/QTc interval, inhibit metabolizing enzymes and/or transports, or cause electrolyte disturbances, as well as for older drugs for which these effects have recently been established.*

### **Drug-Food Interactions**

#### **Food Effect**

The bioavailability of nilotinib is increased by food. TASIGNA must not be taken in conjunction with food (see **DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**) and should be taken 2 hours after a meal. No food should be consumed for at least one hour after the dose is taken.

For patients who are unable to swallow capsules, the content of each capsule may be dispersed in one teaspoon of applesauce and should be taken immediately. Not more than one teaspoon of

applesauce should be used. Yogurt was shown to result in a significant increase in bioavailability and therefore must be avoided and no food other than applesauce must be used (see **DOSAGE AND ADMINISTRATION**).

Products and juices containing grapefruit, star fruit, pomegranate, Seville oranges and other similar fruits that are known to inhibit CYP3A4 should be avoided at any time.

The absorption of TASIGNA is increased if it is taken with food, resulting in higher serum concentration (see **DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY**).

### **Drug-Herb Interactions**

St. John's Wort is a potent CYP3A4 inducer. Co-administration with TASIGNA may lead to increased TASIGNA metabolism, therefore decreased TASIGNA serum concentrations (see **Drug-Drug Interactions**).

### **Drug-Laboratory Interactions**

Interactions with laboratory tests have not been established.

### **Drug-Lifestyle Interactions**

#### **Effects on ability to drive and use machines**

No studies on the effects of nilotinib on the ability to drive and operate machines have been performed. Patients experiencing dizziness, visual impairment or other undesirable effects with a potential impact on the ability to safely drive or use machines should refrain from these activities as long as these undesirable effects persist (see **ADVERSE REACTIONS**).

#### **Alcohol**

No studies have been performed on the potential interaction between nilotinib and alcohol consumption. There is a single report of reduced efficacy of nilotinib in a patient concomitantly consuming alcohol.

## **DOSAGE AND ADMINISTRATION**

### **Dosing Considerations**

#### **Patients with renal impairment**

Clinical studies have not been performed in patients with impaired renal function. Clinical studies have excluded patients with serum creatinine concentration >1.5 times the upper limit of the normal range.

TASIGNA and its metabolites are not renally excreted (See **Pharmacokinetics**).

#### **Patients with hepatic impairment**

Hepatic impairment has an effect on the pharmacokinetics of nilotinib. Dose adjustment is not considered necessary in hepatically impaired patients. Patients with hepatic impairment should

be treated with caution and careful clinical monitoring, including close monitoring of the QTc interval (see **WARNINGS AND PRECAUTIONS**).

### **Cardiac disorders**

In clinical studies, newly diagnosed Ph+ CML-CP and imatinib-resistant or -intolerant Ph+ CML-CP and CML-AP patients with any of the following uncontrolled or significant cardiac disease were excluded: recent myocardial infarction, CHF, unstable angina, or clinically significant bradycardia. Imatinib-resistant or -intolerant Ph+ CML-CP and CML-AP patients with complete left bundle branch block and/or right bundle branch block, with left anterior hemiblock, or with bifascicular block were excluded from the study. Newly diagnosed Ph+ CML-CP patients with complete left bundle branch block were also excluded. ECG and cardiac enzyme monitoring were conducted in patients throughout the studies. Caution should be exercised in patients with relevant cardiac disorders (see **WARNINGS AND PRECAUTIONS**).

### **Method of administration**

TASIGNA should be taken twice daily, at approximately 12 hour intervals and must not be taken with food. The capsules should be swallowed whole with water. No food should be consumed for at least 2 hours before the dose is taken and no additional food should be consumed for at least one hour after the dose is taken (see **WARNINGS AND PRECAUTIONS**, and **DRUG INTERACTIONS**).

For patients who are unable to swallow capsules, the content of each capsule may be dispersed in one teaspoon of applesauce and should be taken immediately. Not more than one teaspoon of applesauce should be used. Yogurt was shown to result in a significant increase in bioavailability and therefore must be avoided and no food other than applesauce must be used (see **ACTION AND CLINICAL PHARMACOLOGY**).

### **Recommended Dose and Dosage Adjustment**

TASIGNA is available in two dosage strengths (150 mg and 200 mg).

Treatment with TASIGNA (nilotinib capsules) should be initiated by a physician experienced in the treatment of patients with CML.

In the clinical study, TASIGNA was allowed to be given in combination with hematopoietic growth factors such as erythropoietin or G-CSF if clinically indicated. TASIGNA was also allowed to be given with hydroxyurea (permitted during the first 28 days of treatment, up to 5 g/day for a maximum of 7 days) or anagrelide (permitted during the first 28 days of treatment) if clinically indicated.

### **Recommended Dose:**

*Newly diagnosed Ph+ CML-CP:*

The recommended dose of TASIGNA is 300 mg orally twice daily (see **CLINICAL TRIALS**). Treatment should continue as long as the patient continues to benefit.

*Ph+ CML-CP and CML-AP resistant to or intolerant to at least one prior therapy including imatinib:*

The recommended dose of TASIGNA is 400 mg orally twice daily (see **CLINICAL TRIALS**). Treatment should continue as long as the patient does not show evidence of progression or unacceptable toxicity.

A baseline ECG is recommended prior to initiating therapy with TASIGNA and should be repeated after 7 days and as clinically indicated. Hypokalemia or hypomagnesemia must be corrected prior to TASIGNA administration and potassium and magnesium blood levels should be monitored periodically during therapy, particularly in patients at risk for these electrolyte abnormalities (see **WARNINGS AND PRECAUTIONS**).

### **Dose Adjustments or Modifications**

Due to possible occurrence of Tumour Lysis Syndrome (TLS) it is recommended to measure serum levels of creatinine, uric acid, phosphate, potassium, corrected calcium and LDH prior to the initiation of treatment with TASIGNA in order to assess the risk or presence of TLS and to monitor these parameters during the initial period of treatment with TASIGNA until a significant reduction of tumour cell burden has been achieved. Prophylaxis of TLS such as hydration and treatment of high uric acid levels in patients at risk and treatment of abnormalities subsequent to established TLS is required. Delay of treatment with TASIGNA in case of established TLS must be outweighed in the individual patient against the risk of delayed control of tumour cell proliferation (see **ADVERSE REACTIONS**).

TASIGNA may need to be temporarily withheld and/or dose reduced for hematological toxicities (neutropenia, thrombocytopenia) that are not related to underlying leukemia (see Table 5 below).

**Table 5 Dose Adjustments for Neutropenia and Thrombocytopenia**

<p>Newly diagnosed Ph+ CML in chronic phase at 300 mg twice daily</p> <p>Resistant or intolerant Ph+ CML in chronic phase or accelerated phase CML at 400 mg twice daily</p>	<p>ANC<sup>#</sup> &lt; 1.0 x 10<sup>9</sup>/L and/or platelet counts &lt;50 x 10<sup>9</sup>/L</p>	<ol style="list-style-type: none"> <li>1. Stop TASIGNA, and monitor blood counts.</li> <li>2. Resume within 2 weeks at prior dose if ANC &gt; 1.0x 10<sup>9</sup>/L and/or platelets &gt;50 x 10<sup>9</sup>/L.</li> <li>3. If blood counts remain low a dose reduction to 400 mg once daily may be required.</li> </ol>
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<sup>#</sup>ANC= absolute neutrophil count

**QT interval prolongation:**

**Table 6 Dose Adjustments for QT prolongation**

ECGs with a QTc > 480 msec	<ol style="list-style-type: none"> <li>1. Withhold TASIGNA, and perform an analysis of serum potassium and magnesium, and if below lower limit of normal, correct with supplements to within normal limits. Concomitant medication usage must be reviewed.</li> <li>2. Resume within 2 weeks at prior dose if QTcF returns to &lt; 450 msec and to within 20 msec of baseline.</li> <li>3. If QTcF is between 450 msec and 480 msec after 2 weeks reduce the dose to 400 mg once daily.</li> <li>4. If, following dose-reduction to 400 mg once daily, QTcF returns to &gt;480 msec, TASIGNA should be discontinued.</li> <li>5. An ECG should be repeated approximately 7 days after any dose adjustment.</li> </ol>
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See Table 7 below for dose adjustments for elevations of lipase, amylase, bilirubin, and/or hepatic transaminases (see **ADVERSE REACTIONS**).

**Table 7 Dose Adjustments for selected non-hematologic laboratory abnormalities**

Elevated serum lipase or amylase $\geq$ Grade 3	<ol style="list-style-type: none"> <li>1. Withhold TASIGNA, and monitor serum lipase or amylase</li> <li>2. Resume treatment at 400 mg once daily if serum lipase or amylase return to <math>\leq</math> Grade 1<sup>1</sup></li> </ol>
Elevated Total bilirubin $\geq$ Grade 3	<ol style="list-style-type: none"> <li>1. Withhold TASIGNA, and monitor total bilirubin</li> <li>2. Resume treatment at 400 mg once daily if total bilirubin return to <math>\leq</math> Grade 1</li> <li>3. Total bilirubin levels should be tested frequently or as clinically indicated</li> </ol>
Elevated hepatic transaminases $\geq$ Grade 3	<ol style="list-style-type: none"> <li>1. Withhold TASIGNA, and monitor hepatic transaminases</li> <li>2. Resume treatment at 400 mg once daily if hepatic transaminases return to <math>\leq</math> Grade 1</li> <li>3. Hepatic transaminases levels should be tested frequently or as clinically indicated</li> </ol>

<sup>1</sup> Serum lipase levels should be tested frequently or as clinically indicated



If clinically significant moderate or severe non-hematologic toxicity develops (including medically severe fluid retention), dosing should be interrupted, and may be resumed at 400 mg once daily once the toxicity has resolved. If clinically appropriate, re-escalation of the dose to 300 mg (newly diagnosed Ph+ CML-CP) or 400 mg (resistant or intolerant Ph+ CML-CP and CML-AP) twice daily should be considered (**see ADVERSE REACTIONS and WARNINGS AND PRECAUTIONS**).

Serum lipase elevations were observed. Few of these elevations were associated with clinical symptoms such as abdominal pain or a diagnosis of pancreatitis. There were 5 cases (1.1%) of pancreatitis reported in imatinib-resistant or-intolerant Ph+ CML-CP and CML-AP patients (N=458). In newly diagnosed Ph+ CML-CP 5 (1.8%) and 8 (2.9%) cases of pancreatitis were reported in patients receiving TASIGNA 300 mg twice daily (N=279) and 400 mg twice daily (N=277), respectively. In case lipase elevations are accompanied by abdominal symptoms, doses should be interrupted and appropriate diagnostics should be considered in order to exclude pancreatitis (see **WARNINGS AND PRECAUTIONS**).

### **Missed Dose**

If a dose is missed, the patient should not take an additional dose, but take the next scheduled usual prescribed dose.

### **OVERDOSAGE**

Isolated reports of intentional overdose with nilotinib were reported, where an unspecified number of TASIGNA capsules were ingested in combination with alcohol and other drugs. Events included neutropenia, vomiting and drowsiness. No ECG changes or hepatotoxicity were reported. Outcomes were reported as recovered. One case of accidental overdose in a patient who took a second dose of TASIGNA 400mg shortly after having ingested a first dose of 400 mg. Approximately 8 hours after ingestion, the patient reported feeling weak, abdominal pain, tachycardia and epistaxis.

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

*For management of a suspected drug overdose, contact your regional Poison Control Centre.*

### **ACTION AND CLINICAL PHARMACOLOGY**

#### **Mechanism of Action**

Pharmacotherapeutic group: Antineoplastic agents - Protein-tyrosine kinase inhibitor ATC code: L01XE08.

TASIGNA is a potent and selective inhibitor of the ABL tyrosine kinase activity of the BCR-ABL oncoprotein both in cell lines and in primary Philadelphia-chromosome positive leukemia

cells. The drug binds strongly within the ATP-binding site in such a manner that it is a potent inhibitor of wild-type BCR-ABL and maintains activity against 32/33 imatinib-resistant mutant forms of BCR-ABL with the T315I mutant being the exception. As a consequence of this biochemical activity, nilotinib selectively inhibits the proliferation and induces apoptosis in cell lines and in primary Philadelphia-chromosome positive leukemia cells from CML patients. In murine models of CML, as a single agent nilotinib reduces tumour burden and prolongs survival following oral administration.

TASIGNA has also little or no effect against the majority of other protein kinases examined, except for PDGFR $\alpha$ , PDGFR $\beta$ , Kit CSF-1R, DDR-1 and DDR-2 and Ephrin receptor kinases which it inhibits at concentrations within the range achieved following oral administration at therapeutic doses recommended for the treatment of CML (see Table 8).

**Table 8 Kinase Profile of nilotinib (Phosphorylation IC<sub>50</sub> nM)**

BCR-ABL	PDGFR	KIT
20	69	210

### Pharmacodynamics

A dose response in the Phase IA component of Study 2101 was explored using the following initial dose cohorts based on daily exposure to nilotinib. The twice daily doses were associated with higher exposures as compared to the once daily doses (See Table 9 below).

**Table 9 Dose and corresponding exposure in all patients or CML-AP patients**

Group	Initial dose (mg)	Nilotinib Regimen	Exposure	Steady-state (day 15) AUC <sub>0-24h</sub> (ng·h/mL)	
				All patients <sup>a)</sup>	CML-AP patients <sup>b)</sup>
1	50-200	once daily	Low	6880 (4750)	6610 (2350-14600)
2	400-1200	once daily	Middle	26000 (13800)	24900 (5770-65900)
3	400	twice daily	High	36000 (11800)	35200 (14600-61000)
4	600	twice daily	High	32800 (13800)	28900 (16000-61500)

<sup>a)</sup> Mean (SD) of dose group

<sup>b)</sup> Median (range) of dose group

### Pharmacokinetics

**Table 10 Summary of nilotinib's pharmacokinetic parameters in serum plasma after a single 400 mg oral dose in healthy male volunteers (n=4)<sup>1</sup>**

t <sub>max</sub>	C <sub>max</sub>	t <sub>1/2</sub> (h)	AUC <sub>0-∞</sub>	Clearance (CL/F)	Volume of distribution (V <sub>z</sub> /F)
3.5 hours	599 ng/mL	17 hours	20700 ng.h/mL	29.1 L/hour	579 L

<sup>1</sup> values are median for t<sub>max</sub> and mean for all others

### **Absorption:**

Peak concentrations of nilotinib are reached 3 hours after oral administration. Nilotinib absorption following oral administration was approximately 30%. The absolute bioavailability of nilotinib has not been determined.

In healthy volunteers, C<sub>max</sub> and area under the serum concentration-time curve (AUC) of nilotinib are increased by 112% and 82%, respectively compared to fasting conditions when TASIGNA is given with food. Administration of TASIGNA 30 minutes or 2 hours after food increased bioavailability of nilotinib by 29% or 15%, respectively (see **DOSAGE AND ADMINISTRATION**, and **DRUG INTERACTIONS**). Nilotinib absorption (relative bioavailability) was reduced by approximately 48% and 22% in patients with total gastrectomy and partial gastrectomy, respectively. Mean steady state trough concentration of nilotinib in patients with total gastrectomy was 599 ng/mL vs. 1035 ng/mL in patients without prior GI resection.

In healthy subjects, single dose administration of 400 mg of nilotinib, using 2 capsules of 200 mg whereby the content of each capsule was dispersed in one teaspoon of applesauce, was shown to be bioequivalent with a single dose administration of 2 intact capsules of 200 mg.

### **Distribution:**

Blood-to-plasma ratio of nilotinib is 0.68. Plasma protein binding is approximately 98% on the basis of *in vitro* experiments.

### **Metabolism:**

Main metabolic pathways identified in healthy subjects are oxidation and hydroxylation. Nilotinib is the main circulating component in the serum. None of the metabolites contribute significantly to the pharmacological activity of nilotinib.

### **Excretion:**

After a single dose of radiolabelled nilotinib in healthy subjects, greater than 90% of the dose was eliminated within 7 days mainly in feces. Parent drug accounted for 69% of the dose.

The apparent elimination half-life estimated from the multiple dose PK with daily dosing was approximately 17 hours. Inter-patient variability in nilotinib PK was moderate to high.

### **Linearity / non-linearity**

Steady-state nilotinib exposure was dose-dependent with less than dose-proportional increases in systemic exposure at dose levels higher than 400 mg given as once daily dosing. Daily systemic exposure to nilotinib of 400 mg twice-daily dosing at steady state was 35% higher than with 800 mg once-daily dosing. Systemic exposure (AUC) of nilotinib at steady state at a dose level of 400 mg twice daily was approximately 13.4% higher than with 300 mg twice daily, based on a full pharmacokinetic profile comparison. The average nilotinib trough and peak concentrations over 12 months, obtained from 275 patients in the nilotinib 300 mg twice daily and 267 patients in the nilotinib 400 mg twice daily, were approximately 15.7% and 14.8% higher following 400 mg

twice daily dosing compared to 300 mg twice daily. There was no relevant increase in exposure to nilotinib when the dose was increased from 400 mg twice-daily to 600 mg twice-daily.

Steady-state conditions were essentially achieved by day 8. An increase in serum exposure to nilotinib between the first dose and steady state was approximately 2-fold for daily dosing and 3.8-fold for twice-daily dosing.

### **Special Populations and Conditions:**

**Effect of age or gender on PK:** Age, body weight, or ethnic origin do not significantly affect the pharmacokinetics of nilotinib, whereas there is an effect of gender, with exposure to nilotinib in female patients being approximately 20% greater than in male patients.

**Pharmacogenomics:** TASIGNA can lead to elevated bilirubin levels. A pharmacogenetic analysis of 101 imatinib-resistant or -intolerant Ph+ CML-CP and CML-AP patients was conducted to evaluate the polymorphisms of UGT1A1 and its potential association with hyperbilirubinemia during TASIGNA treatment. In this study, the (TA)7/(TA)7 genotype was associated with a statistically significant increase in the risk of hyperbilirubinemia relative to the (TA)6/(TA)6 and (TA)6/(TA)7 genotypes. The largest increases in bilirubin were observed in patients with the (TA)7/(TA)7 genotype. Caution is recommended in patients with (TA)7/(TA)7 genotype. (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

**Patients with hepatic impairment:** Hepatic impairment has an effect on the pharmacokinetics of TASIGNA. Single dose administration of TASIGNA 200 mg resulted in increases in AUC of 35%, 35% and 56% in subjects with mild, moderate and severe hepatic impairment, respectively, compared to a control group of subjects with normal hepatic function. The steady-state C<sub>max</sub> of TASIGNA will likely to be increased by up to approximately 29% in subjects with hepatic impairment (see **DOSAGE AND ADMINISTRATION**).

## **STORAGE AND STABILITY**

Store at room temperature (15-30°C).

Store in the original package.

TASIGNA must be kept out of reach and sight of children.

## **SPECIAL HANDLING INSTRUCTIONS**

No special requirements.

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

*TASIGNA (nilotinib capsules) 150 mg Hard Capsules:*

Each capsule contains 150 mg nilotinib base (as hydrochloride, monohydrate).

White to yellowish powder in red opaque hard gelatin capsules, size 1 with black axial imprint “NVR/BCR”.

*Non- medicinal Ingredients:*

Capsule content: Colloidal silicon, anhydrous; Crospovidone; Lactose monohydrate; Poloxamer 188; Magnesium stearate.

Capsule shell: Gelatin; Titanium dioxide (E 171); Iron oxide, red (E 172), Iron oxide, yellow (E 172).

Printing ink: includes black (E 172) iron oxide.

*TASIGNA (nilotinib capsules) 200 mg Hard Capsules:*

Each capsule contains 200 mg nilotinib base (as hydrochloride, monohydrate).

White to yellowish powder in light yellow opaque hard gelatin capsules, size 0 with red axial imprint “NVR/TKI”.

*Non- medicinal Ingredients:*

Capsule content: Colloidal silicon anhydrous; Crospovidone; Lactose monohydrate; Poloxamer 188; Magnesium stearate.

Capsule shell: Gelatin; Titanium dioxide; Iron oxide, yellow.

Printing ink: includes red iron oxide.

Availability of Dosage Forms:

TASIGNA (nilotinib capsules) 150 mg Capsules are supplied in blister packs (7 strips of 4 blisters/card, 4 cards/carton).

TASIGNA (nilotinib capsules) 200 mg Capsules are supplied in blister packs (7 strips of 4 blisters/card, 4 cards/carton).

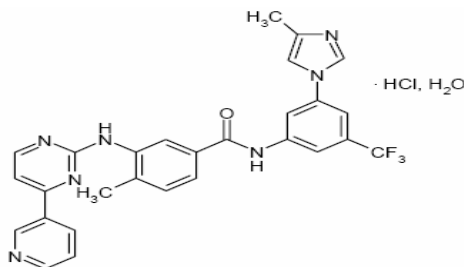
## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

Common name:	Nilotinib hydrochloride monohydrate	
Chemical name:	4-Methyl-N-[3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl]-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzamide, monohydrochloride, monohydrate	
	4-Methyl-N-[3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl]-3-[(4-pyridin-3-yl)pyrimidin-2-yl]amino]benzamide hydrochloride hydrate	
Molecular formula:	Salt form as monohydrate:	$C_{28}H_{22}F_3N_7O \cdot HCl \cdot H_2O$
	Salt form on anhydrous basis:	$C_{28}H_{22}F_3N_7O \cdot HCl$
	Nilotinib base:	$C_{28}H_{22}F_3N_7O$
Molecular mass:	Salt form as monohydrate:	583.99
	Salt form on anhydrous basis:	565.98
	Nilotinib base:	529.52

Structural formula:



#### Physicochemical properties:

Physical Description:	White to slightly yellowish or slightly greenish yellowish powder.
Solubility:	Solubility of nilotinib hydrochloride monohydrate in aqueous solutions strongly decreases with increasing pH, and that nilotinib hydrochloride monohydrate is practically insoluble in buffer solutions of pH 4.5 and

higher pH values. Nilotinib hydrochloride monohydrate is very soluble in dimethyl sulfoxide, sparingly soluble in ethanol and methanol, very slightly soluble in acetonitrile and n-octanol.

**pH:** The pH value of a 0.02% solution of nilotinib hydrochloride monohydrate in water/ethanol 50:50 (V/V) was found to be 4.3. The pH value of a 0.1% suspension of nilotinib hydrochloride monohydrate in water was determined to be 5.3.

**pKa:**  $pK_{a1} = 2.1$ , and  
 $pK_{a2} = 5.4$ .

**Partition Coefficient:** The distribution coefficient for nilotinib hydrochloride monohydrate in n-octanol/0.1N HCl buffer at  $37.0 \pm 0.5^\circ\text{C}$  was determined to be 0.08.

**Melting point:** Nilotinib hydrochloride monohydrate may undergo dehydration prior to melting, therefore no range can be defined.

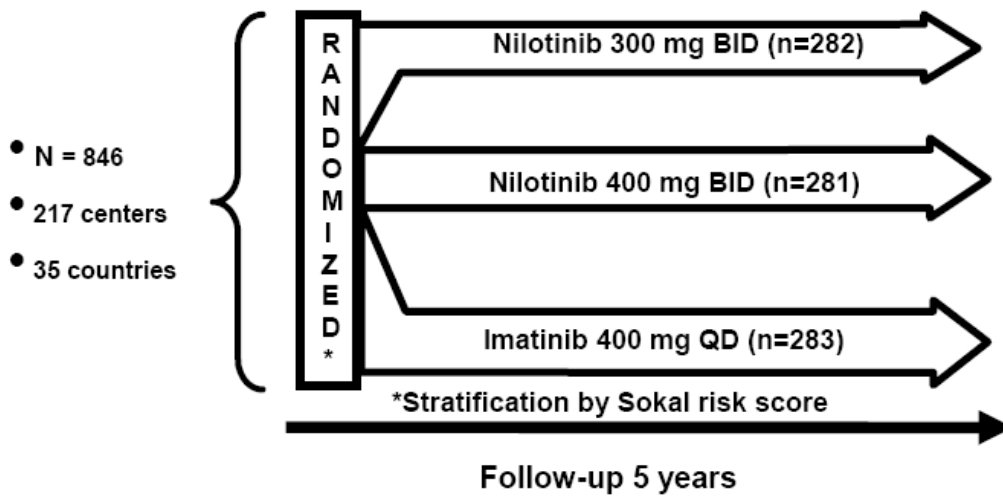
## CLINICAL TRIALS

### Newly diagnosed Ph+ CML-CP

#### *Study demographics and trial design*

The clinical efficacy of nilotinib in newly diagnosed Ph+ CML-CP patients, has been demonstrated based on the Phase III Study (A2303). The design of the study is illustrated in Figure 1.

Figure 1.





**Table 11 Summary of patient demographics for clinical trials (Newly diagnosed Ph+ CML-CP patients exposed to study drug)**

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
A2303	Open label, multicenter, randomized Phase III study was conducted to determine the efficacy of TASIGNA versus GLEEVEC in adult patients with cytogenetically confirmed newly diagnosed Ph+ CML-CP.	<p>nilotinib and imatinib were administered orally:</p> <p>imatinib 400 mg once daily</p> <p>nilotinib 300 mg twice daily</p> <p>nilotinib 400 mg twice daily</p> <p>Median time on treatment was approximately 60 months in all three treatment groups.</p>	<p>Total number of patients randomized = 846</p> <p>imatinib 400 mg once daily (n=283)</p> <p>nilotinib 300 mg twice daily (n= 282)</p> <p>nilotinib 400 mg twice daily (n=281)</p>	<p>imatinib 400 mg once daily 12.4% ≥ 65 years of age Mean: 47(18-80)</p> <p>nilotinib 300 mg twice daily 12.8% ≥ 65 years of age Mean: 47 (18-85)</p> <p>nilotinib 400 mg twice daily 10.0% ≥ 65 years of age in Mean: 47 (18-81)</p>	<p>imatinib 400 mg once daily M=55.8% F=44.2%</p> <p>nilotinib 300 mg twice daily M=56.0% F=44.0%</p> <p>nilotinib 400 mg twice daily M=62.3% F=37.7%</p>

An open label, multicenter, randomized Phase III study (A2303) was conducted to determine the efficacy of TASIGNA versus imatinib in adult patients with cytogenetically confirmed newly diagnosed Ph+CML-CP. Patients were within six months of diagnosis and were previously untreated for CML-CP, except for hydroxyurea and/or anagrelide (See Table 12). In addition, patients were stratified according to Sokal risk score at time of diagnosis.

Baseline characteristics were well balanced between the groups (Table 11). There were slightly more male than female patients in all groups. More than 60% of all patients were Caucasian, and 25% were Asian. Table 12 displays the disease history characteristics.

The primary data analysis time point was when all 846 patients completed 12 months of treatment (or discontinued earlier). Subsequent analyses reflect when patients completed 24, 36, 48 and 60 months of treatment (or discontinued earlier). The median time on treatment is approximately 60 months in all three treatment groups.

The median actual dose intensity was 400 mg/day in the imatinib group, 593 mg/day in the nilotinib 300 mg twice daily group. This study is on-going. Table 13 displays the duration of exposure with TASIGNA.

**Table 12 CML Disease History Characteristics**

	<b>TASIGNA 300 mg twice daily N=282</b>	<b>GLEEVEC 400 mg once daily N=283</b>
Median time since diagnosis of CML in days (range)	31.0 (0-182)	28.0 (1-183)
Hydroxyurea	216 (76.6%)	201 (71.0%)
Anagrelide	6 (2.1%)	4 (1.4%)

**Table 13 Duration of Exposure with TASIGNA**

	<b>TASIGNA 300 mg twice daily N=279</b>	<b>GLEEVEC 400 mg once daily N=277</b>
Median duration of therapy in months (95% CI)	60.02 (59.20-60.42)	58.69 (52.21-59.99)

**Study Results:****Primary Efficacy Endpoint: Major Molecular Response (MMR)**

The primary efficacy variable was MMR at 12 months after the start of study medication. MMR was defined as  $\leq 0.1\%$  BCR-ABL/ABL % by international scale measured by Real-Time Quantitative PCR (RQ-PCR), which corresponds to a  $\geq 3$  log reduction of BCR-ABL transcript from standardized baseline.

The primary efficacy endpoint, MMR rate at 12 months was statistically significantly superior in the nilotinib 300 mg twice daily group compared to the imatinib 400 mg once daily group (44.3% vs. 22.3%,  $p < 0.0001$ ) (Table 14).

At the nilotinib recommended dose of 300 mg twice daily, the rates of MMR at 3, 6, 9 and 12 months was 8.9%, 33.0%, 43.3% and 44.3%, respectively. In the imatinib 400 mg once daily group, the rates of MMR at 3, 6, 9 and 12 months was 0.7%, 12.0%, 18.0% and 22.3%.

The MMR rates at 12, 24, 36, 48, and 60 months is presented in Table 14.

**Table 14 MMR rate**

	<b>TASIGNA 300 mg twice daily N=282* n (%)</b>	<b>GLEEVEC 400 mg once daily N=283* n (%)</b>
<b>MMR at 12 months<sup>2</sup></b> 95% CI for response	125(44.3) <sup>1</sup> [38.4, 50.3]	63(22.3) [17.6, 27.6]
<b>MMR at 24 months<sup>2</sup></b> 95% CI for response	174 (61.7) <sup>1</sup> [55.8, 67.4]	106 (37.5) [31.8, 43.4]
<b>MMR at 36 months<sup>2</sup></b> 95% CI for response	165 (58.5) <sup>1</sup> [52.5, 64.3]	109 (38.5) [32.8, 44.5]
<b>MMR at 48 months<sup>2</sup></b> 95% CI for response	169 (59.9) <sup>1</sup> [54.0,65.7]	124 (43.8) [38.0,49.8]
<b>MMR at 60 months<sup>2</sup></b> 95% CI for response	177 (62.8) [56.8,68.4]	139 (49.1) [43.2,55.1]

\* Denominator for this analysis (N) includes all randomized patients, whether evaluable or not evaluable for MMR

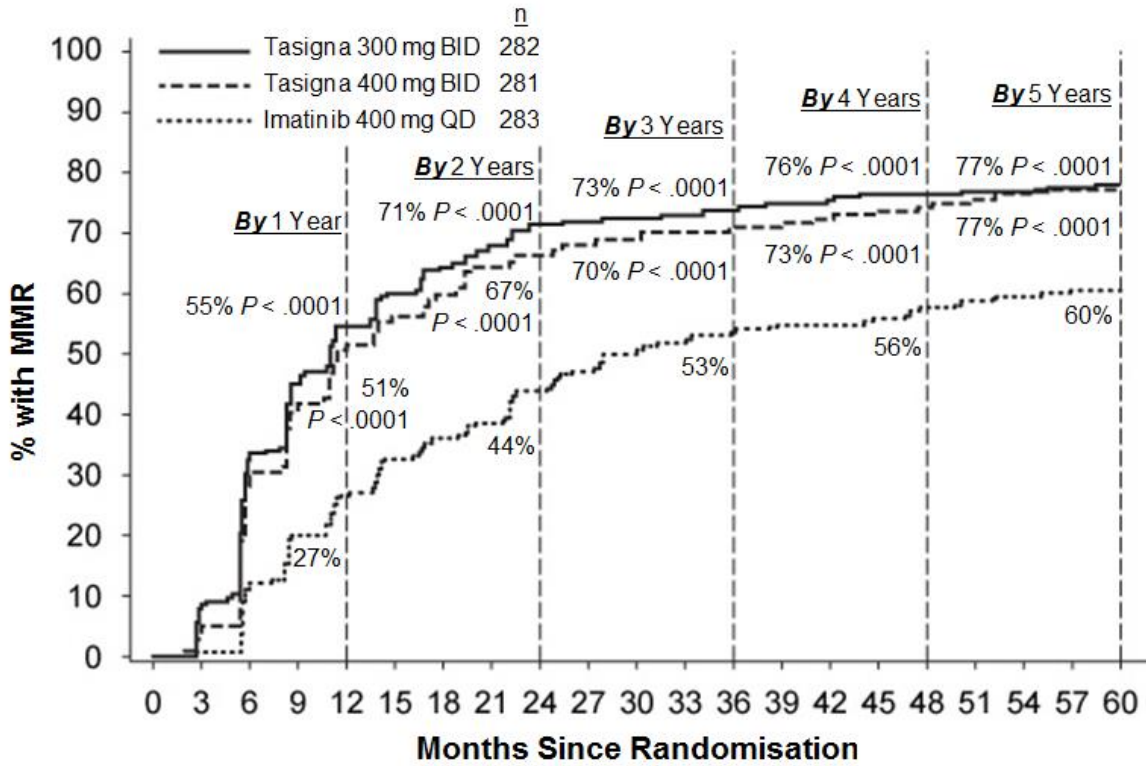
<sup>1</sup> CMH test p-value for response rate (vs. Imatinib 400 mg) <0.0001

<sup>2</sup> Only patients who were in MMR at a specific time point are included as responders for that time point. Other randomized patients, whether evaluable or not at that time point, are conservatively considered as not MMR:

- A total of 129 (15.2%) of all patients were not evaluable for MMR at 12 months (40 in the nilotinib 300 mg BID group, 41 in the nilotinib 400 mg BID group and 48 in the imatinib group) due to missing/not evaluable PCR assessments (n=3), atypical transcripts at baseline (n=8), or discontinuation prior to the 12-month time point (n=118).
- A total of 211 (24.9%) of all patients were not evaluable for MMR at 24 months (68 in the nilotinib 300 mg BID group, 61 in the nilotinib 400 mg BID group and 82 in the imatinib group) due to missing/ not evaluable PCR assessments (n=13), atypical transcripts at baseline (n=8), or discontinuation prior to the 24-month time point (n=190).
- A total of 199 (35.2%) of all patients were not evaluable for MMR at 36 months (87 in the nilotinib 300 mg BID group and 112 in the imatinib group) due to missing/ not evaluable PCR assessments (n=17), atypical transcripts at baseline (n=7), or discontinuation prior to the 36-month time point (n=175).
- A total of 305 (36.1%) of all patients were not evaluable for MMR at 48 months (98 in the nilotinib 300 mg BID group, 88 in the nilotinib 400 mg BID group and 119 in the imatinib group) due to missing/ not evaluable PCR assessments (n=18), atypical transcripts at baseline (n=8), or discontinuation prior to the 48-month time point (n=279).
- A total of 322 (38.1%) of all patients were not evaluable for MMR at 60 months (99 in the nilotinib 300mg BID group, 93 in the nilotinib 400 mg BID group and 130 in the imatinib group) due to missing/ not evaluable PCR assessments (n=9), atypical transcripts at baseline (n=8), or discontinuation prior to the 60-month time point (n=305).

MMR rates by different time points (including patients who achieved MMR at or before those time points as responders) are presented in the cumulative incidence of MMR (Figure 2).

**Figure 2 Cumulative Incidence of MMR**



For all Sokal risk groups, the MMR rates at all timepoints remained consistently higher in the 300 mg twice daily nilotinib group than in the imatinib group.

In an exploratory analysis, 91% (234/258) of patients on nilotinib 300 mg twice daily achieved BCR-ABL levels  $\leq 10\%$  at 3 months of treatment compared to 67% (176/264) of patients on imatinib 400 mg once daily.

Based on the Kaplan-Meier analyses of time to first MMR among all patients, the probability of achieving MMR at different time points was higher in the nilotinib group compared to the imatinib group (HR=2.20 and stratified log-rank  $p < 0.0001$  between nilotinib 300 mg twice daily and imatinib).

**Table 15 Best overall BCR-ABL ratio rates (by 60 months cut-off) – Study CAMN107A2303 (FAS)**

	<b>TASIGNA 300 mg twice daily N=282</b>	<b>GLEEVEC 400 mg once daily N=283</b>
<b>BCR-ABL ratio categories<sup>1</sup></b>		
≤0.0032%	156 (55.3%)	92 (32.5%)
>0.0032% - ≤0.01%	31 (11%)	28 (9.9%)
>0.01 - ≤0.1 %	31 (11%)	53 (18.7%)
>0.1 - ≤1 %	28 (9.9%)	43 (15.2%)
>1 - ≤10 %	15 (5.3%)	26 (9.2%)
>10 %	12 (4.3%)	32 (11.3%)

<sup>1</sup>Molecular response of >0.01 - ≤0.1 %, >0.0032-≤ 0.01% and ≤ 0.0032% by International Scale (IS) corresponds to a ≥3 log to <4 log reduction; a ≥ 4 log to <4.5 log reduction and ≥ 4.5 log reduction, respectively, of BCR-ABL transcripts from a standardized baseline.

Patients categorized according to their best overall BCR-ABL ratio achieved are summarized in Table 15 above.

The proportions of patients who had a molecular response of ≤ 0.01% and ≤ 0.0032% by International Scale (IS) at different time-points is presented in Table 16.

**Table 16 Proportions of patients who had molecular response of ≤ 0.01% (4 log reduction and ≤ 0.0032% (4.5 log reduction)**

	<b>TASIGNA 300 mg twice daily N=282 (%)</b>		<b>Imatinib 400 mg once daily N=283 (%)</b>	
	<b>≤ 0.01%</b>	<b>≤ 0.0032%</b>	<b>≤ 0.01%</b>	<b>≤ 0.0032%</b>
At 12 months	11.7	4.6	3.9	0.4
At 24 months	24.5	12.4	10.2	2.8
At 36 months	29.4	13.8	14.1	8.1
At 48 months	33.0	16.3	19.8	10.2
At 60 months	47.9	32.3	31.1	19.8

### *Duration of MMR*

Based on Kaplan-Meier estimates of the duration of first MMR, the proportions of patients who achieved MMR and were maintaining response for 60 months among patients who achieved MMR were 93.4% (95% CI: 89.9% to 96.9%) in the nilotinib 300 mg twice daily group, and 89.1% (95% CI: 84.2% to 94.0%) in the imatinib 400 mg once daily group.

### Secondary Efficacy Endpoint: Complete Cytogenetic Response (CCyR)

CCyR was defined as 0% Ph+ metaphases in the bone marrow based on a minimum of 20 metaphases evaluated. CCyR rate by 12 months (includes patients who achieved CCyR at or before the 12 month time point as responders) was statistically higher for the nilotinib 300 mg twice daily group compared to imatinib 400 mg once daily group, Table 17.

CCyR rate by 24 months (includes patients who achieved CCyR at or before the 24 month time point as responders) was statistically higher for the nilotinib 300 mg twice daily group compared to imatinib 400 mg once daily group (Table 17).

**Table 17 Rate of Complete Cytogenetic Response (CCyR)**

	<b>TASIGNA 300 mg twice daily N=282 n (%)</b>	<b>GLEEVEC 400 mg once daily N=283 n (%)</b>
<b>By 12 months</b>		
<b>Complete Cytogenetic Response</b>	226 (80.1)	184 (65.0)
95% CI for response	[75.0,84.6]	[59.2,70.6]
<b>CMH test p-value for response rate (vs. imatinib 400 mg)</b>	<0.0001	
<b>By 24 months</b>		
<b>Complete Cytogenetic Response</b>	245 (86.9)	218 (77.0)
95% CI for response	[82.4, 90.6]	[71.7, 81.8]
<b>CMH test p-value for response rate (vs. Imatinib 400 mg)</b>	0.0018	

CMH: Cochran-Mantel-Haenszel

Cytogenetic assessments after 24 months follow-up were not required

### *Duration of CCyR*

Based on Kaplan-Meier estimates, the proportions of patients were maintaining response for 60 months among patients who achieved CCyR were 99.1% (95% CI: 97.9% to 100%) in the nilotinib 300 mg twice daily group, and 97.0% (95% CI: 94.7% to 99.4%) in the imatinib 400 mg once daily group.

### Secondary Efficacy Endpoint: Progression to accelerated phase and blast crisis (AP/BC) on study

Progression “on study” refers to the first documented disease progression to AP/BC or CML-related death that occurred at any time after randomization, up to a 60 month post-treatment follow-up cut-off. Patients receiving nilotinib 300 mg twice daily who had responded insufficiently to study treatment were allowed to increase the dose. Patients receiving imatinib who had responded insufficiently to study treatment were allowed to cross over to nilotinib. By 60 months, in the intention-to-treat (ITT) population, 31 patients progressed to AP/BC (21 in the imatinib group and 10 in the nilotinib 300 mg twice daily group). The estimated rates of patients free from progression to AP/BC at 60 months were 92.1% in the imatinib group and 96.3% in the nilotinib 300 mg twice daily group (HR=0.4636 between nilotinib 300 mg twice daily group and imatinib).

### **BCR-ABL Mutations**

Study A2303 excluded patients with the BCR-ABL T315I mutation at baseline. In this study, BCR-ABL mutation analysis was performed at baseline and post-treatment. Post-treatment mutation analysis was performed only in a subset of patients when warranted by their clinical course. At baseline, no BCR-ABL mutations were detected for any of the 846 patients enrolled in Study A2303. However, Abl polymorphisms were identified at baseline in some patients with equal distribution among the three treatment arms (23 for nilotinib 300 mg twice daily, 20 for nilotinib 400 mg twice daily, and 17 for imatinib). ABL polymorphism were confirmed by amplifying and sequencing the kinase domain region of both non-translocated ABL alleles in the same samples. Polymorphisms have been reported to have no clinical relevance.

At the 60 month follow-up, 12 patients in the nilotinib 300 mg twice daily arm developed mutations, and 10 of the 12 had at least one of the following mutations: T315I, Y253H, E255K, or F359V mutations. One of the 12 patients in the nilotinib 300 mg twice daily arm with E459K mutation progressed. Eleven patients in the nilotinib 400 mg twice daily arm developed mutations, and 2 patients progressed. All 11 patients had one of the following mutations: T315I, Y253H, E255K/V, F359V or Q252H mutations. Twenty-two patients in the imatinib arm developed mutations, and 8 of 22 had one of the following mutations: T315I, Y253H or F359V/C/I or M244V mutations.

The T315I mutation confers a high level of resistance to nilotinib and most tyrosine kinase inhibitors and is associated with rapid disease progression. The Y253H, E255K/V and F359V/C/I mutations are known to be less sensitive to nilotinib.

### Secondary Efficacy Endpoint: Overall survival (OS)

A total of 50 patients died on study, during core treatment, extension treatment or during the follow-up after discontinuation of treatment (18 in the nilotinib 300 mg twice daily group, 10 in the nilotinib 400 mg twice daily group, and 22 in the imatinib 400 mg once daily group). The estimated rates of patients alive at 60 months were 93.7%, versus 91.7%, ( $p = 0.4881$  between nilotinib 300 mg twice daily and imatinib) and 96.2% versus 91.7% ( $p = 0.0266$  between nilotinib

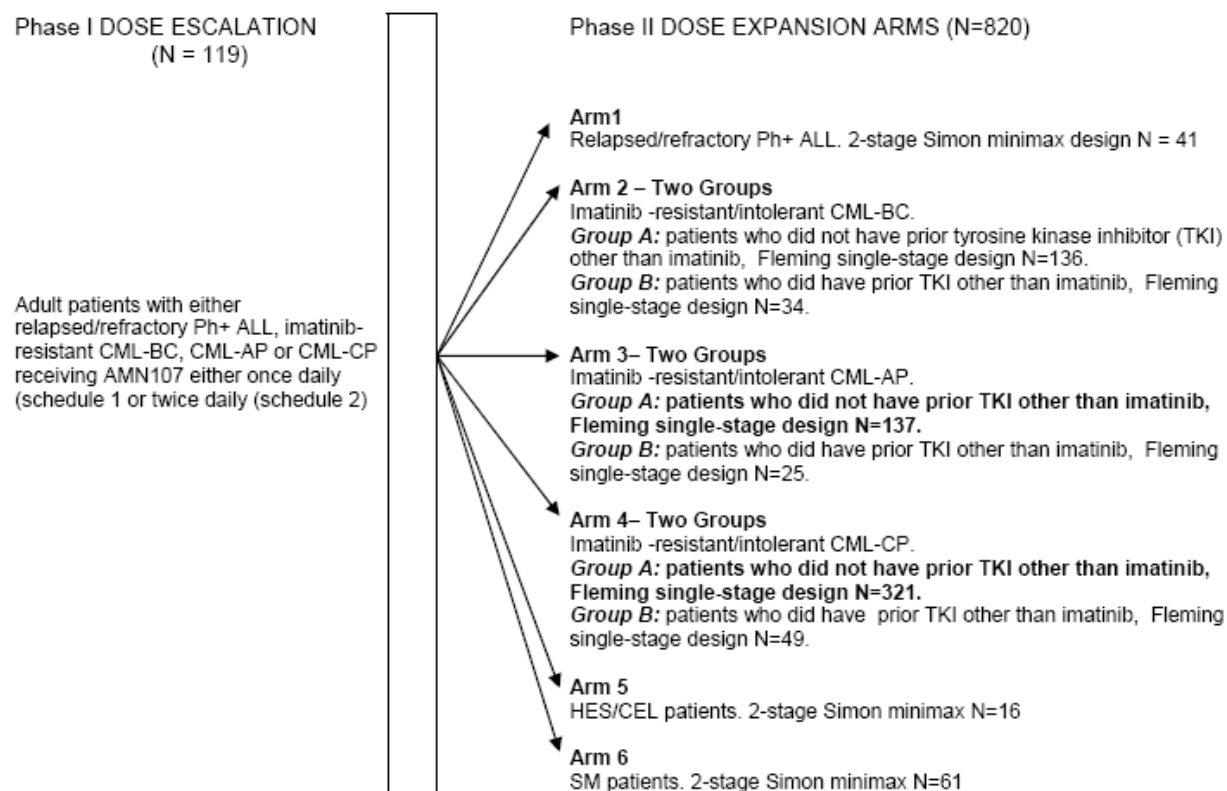
400 mg twice daily and imatinib). As of the 60 month cutoff date, no overall survival benefit has been demonstrated.

## Resistant or intolerant Ph+ CML in chronic phase and accelerated phase

### Study demographics and trial design

The clinical efficacy of nilotinib in imatinib-resistant or -intolerant Ph+ CML in chronic phase (CP) or in accelerated phase (AP) patients, has been demonstrated based on the Phase II component of Study (A2101).

The design of Study A2101 is illustrated in Figure 3 below.





**Table 18 Summary of patient demographics for clinical trials (imatinib-resistant or -intolerant Ph+ CML-AP and CP patients exposed to study drug)**

Study #	Trial design	Dosage, route of administration and median duration	Study subjects (n=number)	Mean age (Range)	Gender
A2101	Open label, multicenter, Phase II study to determine the efficacy of TASIGNA in patients with imatinib-resistant or -intolerant CML with separate treatment arms for chronic and accelerated phase CML.	TASIGNA administered orally: 400 mg twice daily (may be dose-escalated to 600 mg twice daily).  Treatment duration: 561 days for CP and 264 days for AP	CML-CP (Group A) <sup>1</sup> = 321  CML-AP (Group A) <sup>1</sup> = 137	CML-CP (Group A): 31% over the age 65 Mean = 57 Range = 21-85  CML-AP (Group A): 30% over the age 65 Mean = 56 Range=22-82	CML-CP (Group A): M = 50% F = 50%  CML-AP (Group A): M=55% F= 45%

<sup>1</sup>Group A: patients who did not have prior TKI other than imatinib.

An open label, multicenter, Phase II study (A2101) was conducted to determine the efficacy of TASIGNA in patients with imatinib-resistant or -intolerant CML with separate treatment arms for chronic and accelerated phase CML. The study is ongoing. Efficacy was based on 321 CML-CP patients and 137 CML-AP patients enrolled. Median duration of treatment was 561 days and 264 days, respectively (see Table 19). TASIGNA was administered on a continuous basis (twice daily 2 hours after a meal and no additional food for at least one hour), unless there was evidence of inadequate response or disease progression (see Table 18). Dose escalation to 600 mg twice daily was allowed (see Table 18). A total of 57 CML-CP and 33 CML-AP patients were escalated to the 600 mg twice daily dose.

**Table 19 Duration of Exposure with TASIGNA**

	Chronic Phase CML N = 321	Accelerated Phase CML N = 137
Median duration of therapy in days (95% CI)	561 (459-680)	264 (190-357)

**Study Results:**

Resistance to imatinib included failure to achieve a complete hematologic response (by 3 months), cytogenetic response (by 6 months) or major cytogenetic response (by 12 months) or progression of disease after a previous cytogenetic or hematologic response. Imatinib intolerance

included patients who discontinued imatinib because of toxicity and were not in major cytogenetic response at time of study entry.

Overall, 70% of CML-CP patients were imatinib-resistant while 30% were imatinib-intolerant. Overall, 80% of CML-AP patients were imatinib-resistant while 20% were imatinib-intolerant. Prior treatment included imatinib, hydroxyurea, interferon, and stem cell transplant (Table 20). The median highest prior imatinib dose had been 600 mg/day for CP and AP patients. The highest prior imatinib dose was  $\geq 600$  mg/day in 72% of all CML-CP patients and 79% of all CML-AP patients. Thirty-eight (38%) of all CML-CP patients and 45% of all CML-AP patients received imatinib doses  $\geq 800$  mg/day.

**Table 20 CML Disease History Characteristics**

	<b>Chronic Phase (n = 321)</b>	<b>Accelerated Phase (n = 137)<sup>&amp;</sup></b>
Median time since diagnosis in months (range)	58 (5-275)	71 (2-298)
Imatinib		
Resistant	226 (70%)	-
Resistant without MCyR	-	109 (80%)
Intolerant without MCyR	95 (30%)	27 (20%)
Median time of imatinib treatment in days 95%CI	975 (892-1068)	857 (702-1059)
Prior hydroxyurea	83%	91%
Prior interferon	58%	50%
Prior organ transplant	7%	8%

<sup>&</sup> One patient had missing information for imatinib-resistant/intolerant status

The primary endpoint in the CP patients was major cytogenetic response (MCyR), defined as elimination (complete cytogenetic response, CCyR) or significant reduction to  $<35\%$  Ph+ metaphases (partial cytogenetic response, PCyR) of Ph+ hematopoietic cells. The secondary endpoint was complete hematologic response (CHR) in CP patients.

The primary endpoint in the AP patients was overall confirmed hematologic response (HR), defined as either a complete hematologic response (CHR), or no evidence of leukemia (NEL).

**Chronic Phase:** The MCyR rate in 321 CP patients was 59%. Most responders achieved their MCyR rapidly within 3 months (median 2.8 months) of starting TASIGNA treatment and these responses were sustained. The CCyR rate was 44%. The median time to achieve CCyR was just past 3 months (median 3.3 months). Of the patients who achieved MCyR, 77% (95% CI: 71% to 84%) were maintaining response at 24 months. Median duration of MCyR has not been reached. Of the patients who achieved CCyR, 84% (95% CI: 77% to 91%) were maintaining response at 24 months. Median duration of CCyR has not been reached. Patients with a CHR at baseline achieved a MCyR faster (1.4 vs. 2.8 months). Of CP patients without a baseline CHR, 76% achieved a CHR, median time to CHR was 1 month. Median duration of CHR has not been reached. The response rates for the CP treatment arm are reported in Table 21 and Figure 4.

The estimated 24-month overall survival rate in CML -CP patients was 87%.

**Accelerated Phase:** The overall confirmed HR rate in 137 AP patients, was 44%. Median duration of confirmed HR was 21.5 months. Of the patients who achieved HR, 50% (95% CI: 35% to 65%) were maintaining response at 24 months. The rate of confirmed CHR was 31%. Median duration of confirmed CHR was 26.3 months. Of the patients who achieved CHR, 51% (95% CI: 34% to 69%) were maintaining response at 24 months. The unconfirmed MCyR rate was 32% with a median time to response of 2.8 months. Of the patients who achieved MCyR, 66% (95% CI: 50% to 82%) were maintaining response at 24 months. Median duration of MCyR has not been reached. The response rates for the AP treatment arm are reported in Table 21.

The estimated 24-month overall survival rate in CML -AP patients was 70%.

**Table 21 Responses in CML**

(Best Response Rate)	Chronic Phase			Accelerated Phase		
	Intolerant (n = 95)	Resistant (n = 226)	Total (n = 321)	Intolerant (n = 27)	Resistant (n = 109)	Total (n = 137)
<b>Hematologic Response (%)</b>						
Overall (95% CI)	-	-	-	52 (32-71)	41 (32-51)	44 (35-53)
CHR (95% CI)	90% <sup>1</sup> (79-97)	72% <sup>1</sup> (64-79)	76% <sup>1,3</sup> (70-82)	37 <sup>2</sup>	30 <sup>2</sup>	31 <sup>2</sup>
NEL	-	-	-	15 <sup>2</sup>	11 <sup>2</sup>	12 <sup>2</sup>
<b>Unconfirmed<sup>1</sup> Cytogenetic Response (%)</b>						
Major (95% CI)	66% (56-76)	56% (49-63)	59% (54-65)	41 (22-61)	30 (22-40)	32 (24-41)
Complete	51	41	44	30	19	21
Partial	16	15	15	11	11	11

CHR = Complete hematologic response    CCyR = Complete cytogenetic response

NEL = No evidence of leukemia

**Hematologic response: CHR+NEL**

CHR (CML-CP): WBC <10 x 10<sup>9</sup> /L, platelets <450,000/mm<sup>3</sup>, no blasts or promyelocytes in peripheral blood, myelocytes + metamyelocytes <5% in peripheral blood, basophils <5% in peripheral blood, and no extramedullary involvement.

CHR (CML-AP): neutrophils ≥ 1.5 x 10<sup>9</sup>/L, platelets ≥ 100 x 10<sup>9</sup>/L, no myeloblasts in peripheral blood, myeloblast < 5% in bone marrow, basophils <5% in peripheral blood, and no extramedullary involvement.

NEL: same criteria as for CHR but neutrophils ≥ 1.0 x 10<sup>9</sup>/L, platelets ≥ 20 x 10<sup>9</sup>/L without platelet transfusion or bleeding and no requirement for basophils.

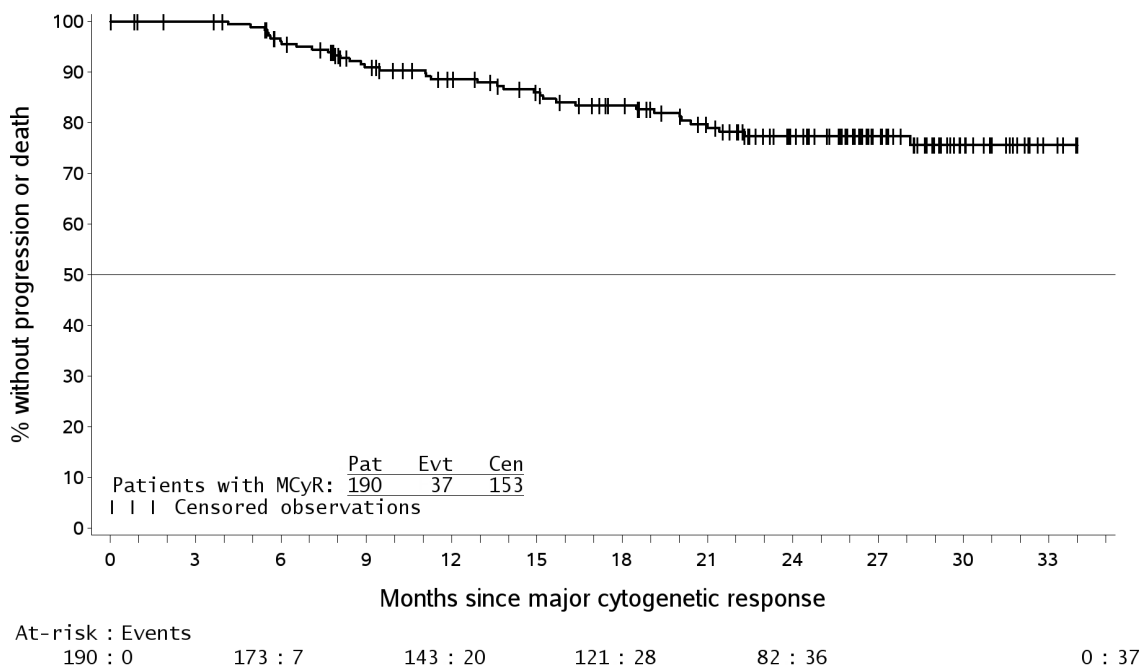
**Cytogenetic response:** Complete (0% Ph+ metaphases) or partial (1-35%). Cytogenetic responses were based on the percentage of Ph-positive metaphases among ≥ 20 metaphase cells in each bone marrow sample.

<sup>1</sup>Unconfirmed: Response based on one assessment

<sup>2</sup>Confirmed: Response assessments confirmed by another assessment at least after 4 weeks).

<sup>3</sup> 207 CP patients did not have a CHR at baseline and were therefore assessable for complete hematologic response of which 158 patients (76%) achieved a CHR

**Figure 4 Kaplan-Meier estimates of duration of MCyR (months)<sup>1</sup> among CML-CP patients who achieved MCyR - Study CAMN107A2101E2 (Conventional ITT population)**



<sup>1</sup>Duration defined as time between first documented response to the date of discontinuation due to progression of disease or death.

Separate treatment arms were also included in the Phase II study (A2101) to study TASIGNA in a group of CP and AP patients who had been extensively pre-treated with multiple therapies, including a tyrosine kinase inhibitor agent in addition to imatinib. Of these patients, 30/36 (83%) were treatment-resistant. In 22 CP patients evaluated for efficacy, TASIGNA induced a 32% MCyR rate and a 50% CHR rate.

After imatinib failure, 24 different BCR-ABL mutations at baseline were noted in 42% of chronic phase and 54% of accelerated phase CML patients who were evaluated for mutations. TASIGNA

demonstrated efficacy in patients harboring a variety of BCR-ABL mutations associated with imatinib resistance, except T315I.

## **DETAILED PHARMACOLOGY**

### **Animal Pharmacodynamics**

Nilotinib has been evaluated in preclinical studies as either the free-base (AMN107-NX) or as a mono-hydrochloride salt (AMN107-AA), and has been developed as an oral formulation of the mono-hydrochloride salt. Both AMN107-NX and AMN107-AA are absorbed following oral administration to animals, and the compound is tolerated at doses showing efficacy in murine myeloproliferative disease models.

*In vitro* and *in vivo* pharmacology studies have been carried out to characterize and define the activity and selectivity of nilotinib (AMN107-NX). For *in vitro* studies both human CML cell lines and murine hematopoietic cells lines have been employed to characterize the antileukemic properties of the compound, and the latter cells have been employed for *in vivo* efficacy studies with nilotinib (both AMN107-NX and AMN107-AA) in mice. To assess selectivity, nilotinib (AMN107-NX) was evaluated for effects on kinase autophosphorylation and cell viability, using either engineered murine Ba/F3 cells, whose survival is dependent on the expression of constitutively activated (oncogenic) kinases, or cancer cell lines expressing the appropriate kinase.

### **Animal Safety pharmacology**

Safety pharmacology studies were conducted to assess the safety of nilotinib in particular organ systems.

#### ***CNS safety pharmacology***

The interactions of nilotinib has been evaluated in a panel of 79 *in vitro* binding assays for potential effects on G-protein coupled receptors, cell transporters, ion channels, nuclear receptors and enzymes. No significant effects on ligand-binding were seen at concentrations < 4.0  $\mu\text{M}$ , other than for the human adenosine 3 receptor ( $\text{IC}_{50}$  values 2.4 and 4.2  $\mu\text{M}$ ) and the human adenosine transporter ( $\text{IC}_{50}$  values 0.9 and 3.5  $\mu\text{M}$ ).

Oral administration of nilotinib at doses up to 300 mg/kg to rats demonstrated no effects on CNS.

#### ***Respiratory effects***

Oral administration of nilotinib at doses up to 300 mg/kg to rats demonstrated no effect on respiratory rate, tidal volume or minute volume.

## ***Cardiovascular effects***

A variety of *in vitro* and *in vivo* studies were conducted to explore possible cardiovascular effects of nilotinib. *In vitro* studies with BJA873 (the nilotinib metabolite, P36.5) were also performed.

*In vitro* cardiac safety studies demonstrated a preclinical signal for QT prolongation. No effects were seen in ECG measurements in dogs or monkeys treated up to 39 weeks or in a special telemetry study in dogs. In neonatal rat ventricular myocytes (NRVM) nilotinib ( $\geq 3.7 \mu\text{M}$ ) increased the ratio of XBP1 mRNA spliced/un-spliced, an endoplasmic reticulum stress marker, but a reduction in cellular ATP content in NRVM was observed at a concentration of  $\geq 11 \mu\text{M}$ . Nilotinib produced increases in heart weights and/or left ventricular mass in rats at 40 mg/kg and 80 mg/kg for 4 weeks treatment without histopathological or structural changes.

## **Animal pharmacokinetics**

The program of nonclinical pharmacokinetics for nilotinib consisted of radiolabeled ADME studies in the species used for chronic toxicity testing (rat and monkey) as well as in mouse, rabbit, and human. Both oral and intravenous dosing routes were evaluated in all species except human (oral dosing only) to allow estimates of absorption and bioavailability to be made. Additional information obtained from the ADME studies included pharmacokinetic parameters of parent drug and total radioactivity, routes and rates of excretion, metabolic pathways, and mass balance. Nilotinib tissue distribution studies were performed in pigmented and non-pigmented rats. The placenta transfer of nilotinib was also investigated in pregnant rats and rabbits. The evaluation of milk excretion of nilotinib was performed in rats. *In vitro* studies with nilotinib were performed to assess blood-plasma distribution, protein binding, phenotyping of enzymes responsible for metabolism, enzyme inhibition and induction, and interactions with drug transporters.

Nilotinib is moderately absorbed in all species tested including human, with relatively high protein binding that is comparable across species. A decrease in the  $\alpha_1$ -acid glycoprotein concentration may, in theory, decrease nilotinib plasma protein binding. However, this effect would be limited due to the significant binding to serum albumin. Nilotinib and/or its metabolites was mainly distributed to adrenal cortex, liver, uveal tract, and small intestine while it showed minimal brain and testis penetration which was consistent with the lack of any toxic effects being observed in these organs. Nilotinib and/or its metabolites showed some passage to the fetus which may account for the incidence of embryolethal and embryotoxicity.

In general, all of the major metabolic pathways observed in humans were also observed in the toxicological test species (mouse, rat, rabbit, and monkey).

Excretion occurred almost exclusively through the fecal route with a minor renal elimination in all species, especially in human. Liver function and drug-drug interactions (enzymes or Pgp) in the liver may affect the elimination of nilotinib.

*In vitro* cytochrome P450 phenotyping experiments indicated that CYP3A4 should be the main enzyme contributing to the oxidative metabolism of nilotinib *in vivo*. Accordingly, a clinical

drug-drug interaction study showed that the metabolism of nilotinib could be reduced by co-administration of the CYP3A4 inhibitor, ketoconazole.

*In vitro* enzyme inhibition studies performed in human liver microsomes revealed that nilotinib could act as an inhibitor of CYP2C8, CYP2C9, CYP2D6, and CYP3A4/5 activity in the clinic and possibly, but less likely, CYP2C19. Nilotinib displayed no potential for time-dependent inhibition (i.e., no mechanism-based inactivation) of any of these enzymes.

Experiments examining the effect of increasing concentrations of nilotinib on bilirubin and estradiol glucuronidation activity suggest that nilotinib could inhibit the activity of UGT1A1 in the clinic. Enzyme induction studies indicate that nilotinib can be considered to be an *in vitro* inducer of CYP2B6, CYP2C8, and CYP2C9 activities (and possibly, CYP3A4 as well). Nilotinib was also found to be a substrate (efflux ratios  $\approx 4$  at a nilotinib concentration of 6  $\mu\text{M}$ ) for the P-gp transporter as well as a possible inhibitor of P-gp in the clinic.

Exposures were generally proportional to the dose in mice, rats, and rabbits but underproportional in dogs, monkeys, and human. There was no clear evidence of gender differences in the exposure for mice, monkeys and dogs, while for the rat, females showed somewhat higher exposure than males. No clear evidence of accumulation for rats and dogs was observed, while the monkey showed moderate accumulation.

## **TOXICOLOGY**

Nilotinib has been evaluated in single dose toxicity, repeated dose toxicity, genotoxicity, reproductive toxicity, phototoxicity, carcinogenicity (rat and mice) studies.

Repeat-dose toxicity studies were conducted in rodents and non-rodents up to nine months in duration. Nilotinib was generally well tolerated and no toxicities prohibitive for use in humans were identified. The rat and cynomolgus monkey were selected as the rodent and non-rodent species for chronic toxicity testing as both species are used routinely as animal models in toxicity evaluations. All of the major metabolic pathways observed in humans were also observed in the toxicological test species (mouse, rat, rabbit, and monkey). Accordingly, all of the metabolites identified in humans were also detected in one or more of the animal species tested, with the exception of two minor fecal metabolites that accounted for 0.62% and 1.2% of the dose, respectively. There were no glutathione or cysteine-related adducts indicative of reactive metabolite formation detected in any of the species.

### **Single oral dose toxicity study**

No single dose oral toxicity studies were performed.

### **Single-dose intravenous toxicity study**

Nilotinib administered to rats at a single intravenous dose of 9 mg/kg did not induce any toxicologically relevant changes attributable to nilotinib and therefore this dose was considered to be the No-Observed-Adverse-Effect-Level (NOAEL).

Potentially vehicle related lesions were observed after the 14-day recovery period. Several animals which received vehicle alone or together with test item showed minimal acute or subacute focal necrosis in the brain. The distribution was considered consistent with ischemic/hypoxic changes, probably as a result of the volume of drug solution applied. No lesions were observed in animals sacrificed one day after the administration.

### **Repeated dose toxicity**

Repeated dose toxicity studies in mice, rats, dogs and cynomolgus monkeys were conducted as indicated in Table 22 below. The doses presented in this section are expressed in terms of the free base.



**Table 22 Repeated dose toxicity studies**

Species (strain)	Study duration	Route of administration	Dose (mg/kg/day)	Gender and no of animals per group	Study Number
Mouse (OF1) non GLP	2-week tolerability	oral (gavage)	0, 50, 150, 450	5 m in control 6 m at 50, 150 and 450 mg/kg	[02R143]
Mouse [CrI:CD-1 (ICR)] non GLP	4-week range finding	oral (in feed)	0, 20, 60, 180	10 m + 10 f	[0580231]
Rat (CrI:Wist Han) non GLP	Rising dose, day 1, 3 & 5	oral (gavage)	50→250→500	2 m + 2 f	[0370053]
	4 days		750	2 m + 2 f	
Rat (CrI:Wist Han) non GLP	2-week range finding	oral (gavage)	0, 30, 100, 300	5 m + 5 f	[0370138]
Rat (CrI:Wist Han) GLP	4-week + 4-week recovery	oral (gavage)	0, 6, 20, 60	10 m + 10 f 6 m + 6 f for recovery in control and high dose groups	[0370146]
Rat (CrI:Wist Han) GLP	4-week	oral (gavage)	0, 20, 80	10 m + 10 f	[0510076]
Rat (CrI:Wist Han)IGS non GLP	4-week range finding	oral (in feed)	0, 20, 60, 180	6 m + 6 f	[0580230]
Rat (CrI:Wist Han) GLP	26-week + 4-week recovery	oral (gavage)	0, 6, 20, 60	20 m + 20 f 10 m + 10 f for recovery in control and high dose groups	[0580158]
Dog (Beagle) non GLP	Rising dose, day 1, 3 & 5	oral (gavage)	100→300→600	1 m + 1 f	[0370052]
	4 days		600	1 m + 1 f	
Dog (Beagle) non GLP	2-week range finding	oral (gavage)	0, 6, 20, 60	1 m + 1 f 2 m + 2 f in high dose only	[0370139]
Dog (Beagle)	4-week + 4-week	oral (gavage)	0, 5, 15, 45	3 m + 3 f 2 m + 2 f for	[0370147]

GLP	recovery			recovery in control and high dose group	
Monkey (cynomolgus) non GLP	Rising dose, day 1, 3 & 6 8 days	oral (gavage)	100→200→400 600	1 m + 1 f  1 m + 1 f	[0470193]
Monkey (cynomolgus) non GLP	4-week	oral (gavage)	0, 100, 200, 400, 600	1 m + 1 f 2 m + 2 f in high dose group	[0570038]
Monkey (cynomolgus) GLP	39-week + 4-week recovery	oral (gavage)	0, 30, 200, 600	4 m + 4 f 2 m + 2 f for recovery in control and high dose groups	[0580157]

f = female animals; m = male animals

Repeated dose toxicity studies in dogs up to 4 weeks duration and in cynomolgus monkeys up to 9 months duration, revealed the liver as the primary target organ of toxicity of nilotinib. Alterations included increased alanine aminotransferase and alkaline phosphatase activity, and histopathology findings (mainly sinusoidal cell or Kupffer cell hyperplasia/hypertrophy, bile duct hyperplasia and periportal fibrosis). In general the changes in clinical chemistry were fully reversible after a four week recovery period, the histological alterations only showed partial reversibility. Exposures at the lowest dose levels where the liver effects were seen were lower than the exposure in humans at a dose of 800 mg/day. Only minor liver alterations were seen in mice or rats treated up to 26 weeks. Although mainly reversible increases in cholesterol levels were seen in rats, dogs and monkeys, a lack of recovery in serum total cholesterol was observed in one female monkey (no evidence of recovery was apparent during the recovery duration) with a lack of reversibility of morphological liver changes in one male monkey. In the 2-year rat carcinogenicity study, the major target organ for non-neoplastic lesions was the uterus (dilatation, vascular ectasia, hyperplasia endothelial cell, inflammation and/or epithelial hyperplasia).

## Genotoxicity

Genotoxicity studies in bacterial *in vitro* systems and in mammalian *in vitro* and *in vivo* systems with and without metabolic activation did not reveal any evidence for a mutagenic potential of nilotinib.

## Carcinogenesis

In the 2-year rat carcinogenicity study conducted orally at TASIGNA at 5, 15, and 40 mg/kg/day, there was a non-statistically significant increased incidence of uterine hemangiosarcoma, adenocarcinoma and squamous cell carcinoma and an increase in follicular cell adenoma in the thyroid gland (barely reaching statistical significance). Given that the incidence of thyroid

follicular cell adenoma and uterine adenocarcinoma were within the historical control range, the data do not clearly indicate that TASIGNA is carcinogenic in rats.

An increased mortality in female rats given nilotinib at  $\geq 15$  mg/kg/day for up to 104 weeks was observed, which was often associated with gross or microscopic uterine changes. Exposures (in terms of AUC) at the highest dose level were represented approximately 2x to 3x human daily steady state exposure at the nilotinib dose of 800 mg/day.

In the 26-week Tg.rasH2 mouse carcinogenicity study, in which nilotinib was administered at 30, 100 and 300 mg/kg/day, skin papillomas/carcinomas were detected at 300 mg/kg, representing approximately 30 to 40 times (based on AUC) the human exposure at the maximum approved dose of 800 mg/day (administered as 400 mg twice daily). The No-Observed-Effect-Level for the skin neoplastic lesions was 100 mg/kg/day, representing approximately 10 to 20 times the human exposure at the maximum approved dose of 800 mg/day (administered as 400 mg twice daily). The major target organs for non-neoplastic lesions were the skin (epidermal hyperplasia), the growing teeth (degeneration/atrophy of the enamel organ of upper incisors and inflammation of the gingiva/odontogenic epithelium of incisors) and the thymus (increased incidence and/or severity of decreased lymphocytes).

### **Reproductive toxicity studies**

Nilotinib did not induce teratogenicity, but did show embryo- and fetotoxicity at doses which also showed maternal toxicity. Increased post implantation loss was observed in both the fertility study, with treatment of both males and female rats, and in the embryotoxicity study with the treatment of female rabbits. Embryo-lethality and fetal effects (mainly decreased fetal weights, visceral and skeletal variations) in rats and increased resorption of fetuses and skeletal variations in rabbits were present in the embryotoxicity studies. Exposure to nilotinib in females at No-Observed-Adverse-Effect-Levels was generally less or equal to that in humans at 800 mg/day.

In a pre- and postnatal study, the oral administration of nilotinib to female rats from day 6 of gestation to day 21 or 22 post-partum resulted in maternal effects (reduced food consumption and lower body weight gains) and longer gestation period at 60 mg/kg. The maternal dose of 60 mg/kg was associated with decreased pup body weight and changes in some physical development parameters (the mean day for pinna unfolding, tooth eruption and eye opening was earlier). The No-Observed-Adverse-Effect-Level in maternal animals and offspring was a maternal dose of 20 mg/kg.

### **Phototoxicity**

Nilotinib was shown to absorb light in the UV-B and UV-A range, and to be distributed into the skin showing a phototoxic potential *in vitro*. However, no phototoxicity has been observed *in vivo*. Therefore the risk that nilotinib causes photosensitization in patients is considered very low.

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**PART III: CONSUMER INFORMATION**

**PrTASIGNA<sup>®</sup>**  
(Nilotinib Capsules)

150 mg and 200 mg nilotinib  
(as nilotinib hydrochloride monohydrate)

This leaflet is part III of a three-part "Product Monograph" published when TASIGNA was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TASIGNA. Contact your doctor or pharmacist if you have any questions about the drug.

**Read all of this leaflet carefully before you start taking this medicine.**

Keep this leaflet. You may need to read it again.

**ABOUT THIS MEDICATION**

What the medication is used for:

- TASIGNA is indicated for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase.
- TASIGNA is also indicated for the treatment of chronic phase and accelerated phase Philadelphia chromosome positive chronic myeloid leukemia (CML) in adult patients resistant to or intolerant of at least one prior therapy, including imatinib.

What it does:

In patients with CML, a change in DNA (genetic material) triggers a signal that tells the body to produce abnormal white blood cells. TASIGNA blocks this signal, and thus stops the production of these abnormal cells.

When it should not be used:

Do not use TASIGNA if you:

- have an abnormal electrical signal of the heart (prolongation of QT interval),

- have uncorrectable low levels of potassium or magnesium,
- are **allergic** (hypersensitive) to nilotinib or any of the other ingredients of TASIGNA.

What the medicinal ingredient is:

Nilotinib.

What the important nonmedicinal ingredients are:

Crospovidone, lactose monohydrate, magnesium stearate, poloxamer, colloidal silicon anhydrous.

- The 150 mg capsule shell is composed of gelatin, titanium dioxide, iron oxide yellow, iron oxide red and the stamping of the imprint includes black iron oxide.
- The 200 mg capsule shell is composed of gelatin, titanium dioxide, iron oxide yellow and the stamping of the imprint includes red iron oxide.

What dosage forms it comes in:

TASIGNA is supplied as a hard capsule.

Each capsule of 150 mg contains 150 mg of nilotinib (as nilotinib hydrochloride monohydrate) and each capsule of 200 mg contains 200 mg of nilotinib (as nilotinib hydrochloride monohydrate).

- The 150 mg capsules are red. A black imprint is stamped on each capsule ("NVR/BCR").
- The 200 mg capsules are light yellow. A red imprint is stamped on each capsule ("NVR/TKI").

TASIGNA is available in monthly packs:

- The monthly pack contains 112 capsules divided into 4 individual weekly blister-packs.

**WARNINGS AND PRECAUTIONS**

**Serious Warnings and Precautions:**

TASIGNA should be given under the supervision of a doctor experienced in the use of anti-cancer drugs. Serious side effects with TASIGNA include:

- Sudden cardiac deaths,
- Prolongation of the QT interval (abnormal electrical signal of the heart),
- Ischemic heart disease (heart disorder), ischemic, cerebrovascular events (stroke or other problems due to decreased blood flow to the brain) and peripheral arterial occlusive disease (PAOD) (problems with decreased blood flow to your leg), rare fatal cases have been reported,

- Liver toxicity (increase of liver enzymes), fatal cases have been reported,
  - Pancreatitis (inflammation of the pancreas),
  - Myelosuppression (decrease of the production of blood cells).
- TASIGNA should not be used in patients who have uncorrectable low levels of potassium or magnesium.

BEFORE you use TASIGNA talk to your doctor or pharmacist if you:

- have a **heart disorder**, or a heart rhythm disorder (or a family history of heart rhythm disorder) such as an irregular heartbeat or an abnormal electrical signal of the heart called “prolongation of the QT interval”,
- have a personal history of fainting spells,
- have a family history of sudden cardiac death at age of less than 50 years,
- are being **treated with medicines** that affect the heart beat (antiarrhythmics) or medicines that may have an unwanted effect on the function of the heart (QT prolongation) (see also other drugs that may interact with TASIGNA under “*INTERACTIONS WITH THIS MEDICATION*”),
- have electrolyte problems (*e.g.*, low blood potassium levels) or conditions that could lead to electrolyte disturbances (*e.g.*, vomiting, diarrhea, dehydration),
- have an eating disorder or are following a strict diet;
- have diabetes, especially with associated nerve disorders;
- had a stroke or other problems due to decreased blood flow to the brain,
- have problems with decreased blood flow to your legs,
- have liver/kidney disease,
- have had pancreatitis (inflammation of the pancreas),
- have intolerance to lactose (milk sugar). TASIGNA contains lactose,
- are pregnant or plan to get pregnant. TASIGNA is not recommended during pregnancy as it may harm the fetus. Women who can get pregnant must use highly effective birth control during treatment with TASIGNA and at least 4 weeks after ending treatment,
- are a male patient and are concerned about your fertility (ability to father a child),
- are a sexually active male. Men who take TASIGNA must use highly effective birth control during treatment with TASIGNA, and at least 4 weeks after ending treatment.–Tell your doctor right away if your female partner becomes pregnant,
- breast feeding or plan to breast feed. Women should not breast feed while taking TASIGNA,
- have had a surgical procedure involving the removal of the entire stomach (total gastrectomy).

- have ever had or might now have a hepatitis B virus infection (a viral infection of the liver). This is because during treatment with TASIGNA, hepatitis B may become active again, which can be fatal in some cases. Your doctor will check for signs of this infection before and during treatment with TASIGNA.

TASIGNA can cause a possible life-threatening heart problem called QTc prolongation. QTc prolongation causes an irregular heart beat, which may uncommonly (0.17%) lead to sudden cardiac death. These heart rhythm disturbances are more likely in patients with risk factors, such as heart disease, or in the presence of certain interacting drugs. If you experience any symptoms of a possible heart rhythm disturbance, such as dizziness, palpitations (sensation of rapid, pounding, or irregular heart beat), fainting, or seizures, you should seek immediate medical attention.

Blood tests will also monitor the level of fatty substances (cholesterol and lipids) and sugar (glucose) in your blood.

There is no experience with the use of TASIGNA in children and adolescents.

During the treatment with TASIGNA, you will need to have certain tests, including blood tests, to monitor how TASIGNA works.

TASIGNA may cause dizziness. **DO NOT** drive or use machines if you feel dizziness or are unable to see well while taking TASIGNA.

### INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist **before taking TASIGNA** if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This includes in particular:

- antiarrhythmics such as amiodarone, disopyramide, procainamide, quinidine, sotalol, digoxin, ibutilide, flecainide, propafenone - used to treat irregular heart beat;
- verapamil - used to treat high blood pressure and some types of irregular heart beat;
- chloroquine, halofantrine, clarithromycin, haloperidol, moxifloxacin, methadone, bepridil, pimozide - medicines that may have an unwanted effect on the function of the heart (QT prolongation);
- laxatives, enemas, water pills, amphotericin B, high dose corticosteroids - medicines that can disturb electrolyte levels;



- chlorpromazine, droperidol, ziprasidone - used to stabilize thinking and behaviour;
- fluoxetine, citalopram, venlafaxine, tricyclic/tetracyclic antidepressants e.g. amitriptyline, imipramine, maprotiline – used to treat mood disorder;
- pentamidine – used to prevent and treat pneumocystis carinii pneumonia;
- chloroquine – used to treat malaria;
- vorinostat, sunitinib, lapatinib – used to treat cancers;
- salmeterol, formoterol – used to treat asthma;
- ketoconazole, itraconazole, voriconazole, levofloxacin, ciprofloxacin, fluconazole, erythromycin, clarithromycin, telithromycin, tacrolimus, cefazolin - used to treat infections;
- domperidone – used to treat gastrointestinal motility disorder;
- metoclopramide, prochlorperazine, ondansetron and dolasetron- used to treat nausea;
- ritonavir - an anti-HIV medicine from the class “antiproteases”;
- carbamazepine, phenobarbital, phenytoin - used to treat epilepsy;
- rifampicin - used to treat tuberculosis;
- St. John’s Wort - a herbal product (also known as *Hypericum Perforatum*);
- midazolam - used to relieve anxiety before surgery;
- warfarin - used to treat blood coagulation disorders (such as blood clots or thromboses);
- morphine, methadone - used to treat moderate to severe pain;
- buprenorphine- substitute treatment for opioids dependence;
- cyclosporine A- used to prevent organ transplantations rejections, and to treat autoimmune conditions;
- alfentanil and fentanyl - used to treat pain and used as a sedative before or during surgery or medical procedure;
- cyclosporine, sirolimus and tacrolimus - medicines that suppress the “self-defense” ability of the body and fight infections - commonly used to prevent the rejection of transplanted organs such as liver, heart and kidney;
- dihydroergotamine and ergotamine – used to treat dementia;
- levothyroxine– used to treat thyroid deficiency
- statins (such as simvastatin and lovastatin)- class of drugs used to treat high level of fats in blood.

In addition, if you are taking TASIGNA, discuss with your doctor before taking antacids (medicines against heartburn).

These medications need to be taken separately from TASIGNA:

- antacids called H2 blockers which suppress the production of acid in the stomach – should be taken approximately 10 hours before and approximately 2 hours after you take TASIGNA;
- antacids such as those containing aluminum hydroxide, magnesium hydroxide and simethicone which neutralize the high acidity of the stomach – should be taken approximately 2 hours before or approximately 2 hours after you take TASIGNA.

If you need to see other doctors, you should also tell him or her that you are taking TASIGNA.

**Do not take TASIGNA with food.** Take the capsules at least 2 hours after any food and then wait at least 1 hour before eating again. Taking TASIGNA with food may increase the amount of TASIGNA in the blood, possibly to a harmful level.

**Do not take any products or juices containing grapefruit, star fruit, pomegranate, Seville oranges or similar fruits while taking TASIGNA.** This may increase the amount of TASIGNA in blood, possibly to a harmful level.

**If you are unable to swallow capsules,** you may mix the content of each capsule in one teaspoon of applesauce (pureed apple) and swallow the mixture immediately. No other food should be used.

## PROPER USE OF THIS MEDICATION

### Usual dose:

Always take TASIGNA exactly as your doctor has told you.

### **Usual starting dose:**

- Newly diagnosed Ph+CML in chronic phase: 300 mg (2 capsules of 150 mg) twice a day, approximately every 12 hours.
- Chronic phase and accelerated phase Ph+CML in patients who had a previous treatment: 400 mg (2 capsules of 200 mg) twice a day, approximately every 12 hours.

Capsules to be taken orally on an empty stomach, at least two hours after any food and wait at least 1 hour before eating again.

Swallow the capsules whole with water. Do not open the capsules.

**If you are unable to swallow capsules:**

- **Open** the capsules
- **Mix** the content of each capsule in one teaspoon of applesauce (pureed apple)  
Use **only one single teaspoon** of applesauce (not more).  
Use **only applesauce** (no other food).

**Swallow** the mixture **immediately**

Overdose:

If you have taken more TASIGNA than you should have, or if someone else accidentally takes your capsules, contact your doctor or the nearest hospital emergency room or a local poison control centre immediately. You may be asked to show them the pack of capsules.

Missed Dose:

If you miss a dose, take your next dose as scheduled. Do not take a double dose to make up for the forgotten capsules.

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

As with all medicines, TASIGNA can cause side effects. The side effects of TASIGNA are as follows:

**Very common:**

- nausea, constipation, vomiting;
- headache;
- muscle pain, pain in joints;
- itching, rash, hives;
- hair loss;
- tiredness (fatigue).

If any of these affects you severely, tell your doctor.

**Common:**

- upper respiratory tract infections
- abdominal pain, dyspepsia (digestion problems); diarrhea; eating disorder (anorexia), disturbed sense of taste;
- pain (bone and extremity);
- muscle spasms;
- skin reddening, dry skin;
- insomnia, depression, anxiety;
- weakness;
- dizziness, spinning sensation (vertigo).

If any of these affects you severely, tell your doctor.

TASIGNA may also cause:

- a decrease of the production of blood cells (low levels of white cells, red cells, platelets);
- an increased blood level of lipase or amylase (inflammation of the pancreas);
- an increase in liver enzymes (liver dysfunction or toxicity);
- an increased blood level of creatinine (reduced kidney function), and high or low levels of potassium or low level of magnesium.
- an increase of cholesterol and other fats (lipids) in your blood.
- low blood level of insulin (an enzyme regulating blood sugar level).
- an increase of prothrombin time
- a previous hepatitis B virus infection (a viral infection of the liver) to become active again when you have had a hepatitis B infection in the past (hepatitis B virus reactivation), which can be fatal in some cases

If you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Call your doctor as soon as possible if you faint (loss of consciousness) or have an irregular heartbeat while taking TASIGNA as these may be due to a serious heart condition.

<b>SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM</b>			
Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
<b>Very common or common</b> -Fever, easy bruising, frequent Infections (changes in blood test results).		√	
<b>Common</b> -Sensation of tingling, pain or numbness in fingers and toes (paraesthesia).  - Chest pain, or discomfort, high blood pressure, irregular heart rhythm blue discoloration of the lips, tongue or skin (heart disorders).		√	
		√	
-Irregular heartbeat, fainting, loss of consciousness (prolongation of the QT interval). - Abdominal pain. - Fever. -Difficulty breathing or painful, cough, wheezing with or without fever (lung disorders).  - Severe upper (middle or left) abdominal pain (possible signs of inflammation of pancreas)		√	
	√		
	√		
		√	
		√	
<b>Common or uncommon</b> -Rapid weight gain, swelling of hands, ankles, feet or face (signs of water retention).		√	
<b>Uncommon</b> - Yellow skin and eyes, nausea, loss of appetite, dark-colored urine (liver damage).		√	
- Chest pain, irregular heart rhythm (fast or slow) (cardiac failure).		√	
-Diarrhea.	√		
-Vomiting.	√		
-Nausea.	√		

<b>SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM</b>			
Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
-Abdominal pain, nausea, vomiting of blood, black stools, constipation, heartburn, swelling or bloating of the abdomen (gastrointestinal disorders).  - pain or discomfort, weakness, or cramping in leg muscles which may be due to decreased blood flow, ulcers that heal slowly or not at all and noticeable changes in color (blueness or paleness) or temperature (coolness) as these symptoms could be signs of artery blockage in the affected limb (leg or arm) and digits (toes and fingers).		√	
-Generally feeling unwell.	√		
		√	
-Bone pain.		√	
-Pain in joints.		√	
-Excessive thirst, high urine output, increased appetite with weight loss, tiredness (high level of sugar in the blood).		√	
-Difficulty and pain when passing urine, exaggerated sense of needing to urinate, blood in urine (urinary tract disorders).		√	
-Fast heart beat, bulging eyes, weight loss, swelling at front of the neck (overactive thyroid gland).		√	
-Severe headache often accompanied by nausea, vomiting and sensitivity to light (migraine).		√	

<b>SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM</b>			
Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
<b>Uncommon or unknown frequency</b> -Weakness or paralysis of limbs or face, difficulty speaking, severe headache, seeing, feeling or hearing things that are not there, loss of consciousness, confusion, disorientation, trembling (nervous system disorders such as intracranial hemorrhage).  -Thirst, dry skin, irritability, dark urine, decreased urine output (kidney disorders).		√	
		√	
- Blurred vision, loss of vision in eye, increased sensitivity of the eyes to light, eye pain or redness, swelling and itching of the eyelids, decreased sharpness of vision, eye irritation (eye disorders).		√	
-Rash, painful red lumps, pain in joints and muscles (skin disorders).		√	
<b>Unknown frequency</b> -Muscle spasms, fever, red-brown urine (rhabdomyolysis). -Swelling and pain in one part of the body (clotting within a vein). -Weight gain, tiredness, hair loss, muscle weakness, feeling cold (underactive thyroid gland). -Dizziness, spinning sensation (hypotension).  -Second malignancies (such as gastric cancer, gastrointestinal stromal tumour, pancreatic carcinoma, pancreatic neuroendocrine tumour, colon cancer).		√	
		√	
		√	
		√	
		√	

<b>SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM</b>			
Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Nausea, shortness of breath, irregular heartbeat, clouding of urine, tiredness and/or joint pain associated with tumor lysis syndrome (the sudden, rapid death of cancer cells due to the treatment).		√	
-fever, skin rash, joint pain and inflammation as well as tiredness, loss of appetite, nausea, jaundice (yellowing of the skin or whites of eyes), pain in the upper right abdomen, pale stools and dark urine (possible signs of hepatitis B virus reactivation)		√	
<b>Reported from post-marketing with Unknown frequency:</b> -Difficulty breathing, dizziness (severe allergic reaction). -Anxiety, restlessness, chest pain (cardiac tamponade). -Difficulty breathing with wheezing or coughing (bronchospasm).		√	
		√	
		√	
-Excessive thirst, high urine output, increased appetite with weight loss, tiredness (higher level of sugar in the blood).		√	
-Nausea, shortness of breath, irregular heartbeat, clouding of urine, tiredness and/or joint discomfort associated with abnormal laboratory values (such as high potassium, uric acid, and phosphorous levels and low calcium levels in the blood).		√	
-Spontaneous abortions, stillbirth and fetal malformations		√	

*This is not a complete list of side effects. For any unexpected effects while taking TASIGNA, contact your doctor or pharmacist.*

**HOW TO STORE IT**

- Keep out of the reach and sight of children.
- Do not use TASIGNA after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.
- Store at room temperature (15-30°C).
- Store in the original package.

1-800-363-8883

This leaflet was prepared by  
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PrTASIGNA (nilotinib capsules) is a registered trademark.

**REPORTING SUSPECTED SIDE EFFECTS**

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

You can report any suspected adverse reactions associated with the use of health products in the Canada Vigilance Program by one of the following 3 ways:

Report online: [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)

Call toll-free at 1-866-234-2345

Complete a Canada Vigilance Reporting Form and:

- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program  
Health Canada  
Postal Locator 0701D  
Ottawa, ON K1A0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect).

**NOTE:** Should you require information related to the management of the side effect, contact your health care professional. The Canada Vigilance Program does not provide medical advice.

**MORE INFORMATION**

Please consult your doctor or pharmacist with any questions or concerns you may have regarding your individual condition.

This document plus the full product monograph, prepared for health professionals can be found at:  
<http://www.novartis.ca>

or by contacting the sponsor  
Novartis Pharmaceuticals Canada Inc., at: