AUSTRALIAN PRODUCT INFORMATION - TASIGNA®
(nilotinib)

1. NAME OF THE MEDICINE

Nilotinib

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance
TASIGNA capsules contain nilotinib (as hydrochloride, monohydrate) in 150 mg and 200 mg strengths. Nilotinib is a white to slightly yellowish or slightly greenish yellowish powder.

Excipients
TASIGNA contains lactose and may not be suitable for patients that are intolerant to this ingredient (see section 4.4).

For the list of excipients, see section 6.1 List of Excipients.

3. PHARMACEUTICAL FORM

Hard capsules

TASIGNA 150 mg
White to yellowish powder in red opaque hard gelatin size 1 capsules, with black axial imprint NVR/BCR

TASIGNA 200 mg
White to slightly yellowish powder in light yellow opaque hard gelatin size 0 capsules, with red axial imprint NVR/TKI

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TASIGNA is indicated for the:
- treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukaemia (CML) in chronic phase.
- treatment of adults with chronic phase and accelerated phase Philadelphia chromosome positive chronic myeloid leukaemia (CML) resistant to or intolerant of prior therapy including imatinib.

4.2 Dose and method of administration

Therapy should be initiated by a physician experienced in the treatment of patients with CML and should continue as long as the patient continues to benefit.

Dose

Patients with Newly Diagnosed Ph+ CML-CP

The recommended dose of TASIGNA is 300 mg twice daily (see section 5.2 Pharmacokinetic Properties).

Dosage in newly diagnosed Ph+ CML-CP patients who have achieved a sustained deep molecular response (MR 4.5)

Discontinuation of treatment may be considered in eligible Ph+ CML-CP patients who have been treated with TASIGNA at 300 mg twice daily for a minimum of 3 years if a deep molecular response is sustained for a minimum of one year immediately prior to discontinuation of therapy. Discontinuation of TASIGNA should be initiated by a physician experienced in the treatment of patients with CML (see section 4.4 Special warnings and precautions for use and section 5.1 Pharmacodynamic properties, Clinical Trials).

Patients who are eligible to discontinue TASIGNA therapy must have their BCR-ABL transcript levels and complete blood count with differential monitored monthly for one year, then every 6 weeks for the second year, and every 12 weeks thereafter. Monitoring of BCR-ABL transcript levels must be performed with a quantitative diagnostic test validated to measure molecular response levels on the International Scale (IS) with a sensitivity of at least MR4.5 (BCR-ABL/ABL $\leq$0.0032% IS).

For patients who lose MR4.0 (MR4=BCR-ABL/ABL $\leq$0.01%IS) but not Major Molecular Response (MMR; BCR-ABL/ABL $\leq$0.1%IS) during the treatment-free phase, BCR-ABL transcript levels should be monitored every 2 weeks until BCR-ABL levels return to a range between MR4.0 and MR4.5. Patients who maintain BCR-ABL levels between MMR and MR4.0 for a minimum of 4 consecutive measurements can return to the original monitoring schedule.

Patients who lose MMR must re-initiate treatment within 4 weeks of when loss of remission is known to have occurred. TASIGNA therapy should be re-initiated at 300 mg twice daily or at a reduced dose level of 400 mg once daily if the patient had a dose reduction prior to discontinuation of therapy. Patients who re-initiate TASIGNA therapy should have their BCR-ABL transcript levels monitored monthly until MMR is re-established (see section 4.4 Special warnings and precautions for use and section 5.1 Pharmacodynamic Properties, Clinical Trials).

Patients with Ph+CML –CP and CML-Accelerated Phase (AP) Resistant to or Intolerant to at Least One Prior Therapy Including Imatinib

The recommended dose of TASIGNA is 400 mg twice daily (see section 5.2 Pharmacokinetic Properties).

Dosage in Ph+ CML-CP patients who have achieved a sustained deep molecular response (MR 4.5) on TASIGNA following prior imatinib therapy

Discontinuation of treatment may be considered in eligible Ph+ CML-CP patients who have been treated with TASIGNA for a minimum of 3 years if a deep molecular response is sustained for a minimum of one year immediately prior to discontinuation of therapy. Discontinuation of TASIGNA should be initiated by a physician experienced in the treatment

of patients with CML (see section 4.4 Special warnings and precautions for use and section 5.1 Pharmcodynamic Properties, section 5.1 Pharmacodynamic Properties, Clinical Trials).

Patients who are eligible to discontinue TASIGNA therapy must have their BCR-ABL transcript levels and complete blood count with differential monitored monthly for one year, then every 6 weeks for the second year, and every 12 weeks thereafter. Monitoring of BCR-ABL transcript levels must be performed with a quantitative diagnostic test validated to measure molecular response levels on the International Scale (IS) with a sensitivity of at least MR4.5 (BCR-ABL/ABL ≤0.0032% IS).

Patients with confirmed loss of MR 4.0 (two consecutive measures separated by at least 4 weeks showing loss of MR 4.0; BCR-ABL/ABL ≤0.01%IS) or loss of MMR (BCR-ABL/ABL ≤0.1%IS) must re-initiate treatment within 4 weeks of when loss of remission is known to have occurred. TASIGNA therapy should be re-initiated at either 300 mg or 400 mg twice daily. Patients who re-initiate TASIGNA therapy should have their BCR-ABL transcript levels monitored monthly until previous MMR or MR 4.0 is re-established (see section 4.4 Special warnings and precautions for use and section 5.1 Pharmacodynamic Properties, Clinical Trials).

Monitoring Recommendations and Dose Adjustments

A baseline ECG is recommended prior to initiating therapy with TASIGNA and should be repeated after 7 days and as clinically indicated. Hypokalaemia or hypomagnesaemia 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 section 4.4 Special warnings and precautions for use).

Increases in total serum cholesterol levels have been reported with TASIGNA therapy (see section 4.4 Special warnings and precautions for use). Lipid profiles should be determined prior to initiating TASIGNA therapy, assessed at month 3 and 6 after initiating therapy, and at least yearly during chronic therapy.

Increases in blood glucose levels have been reported with TASIGNA therapy (see section 4.4 Special warnings and precautions for use). Blood glucose levels should be assessed prior to initiating TASIGNA therapy and monitored during treatment.

Due to possible occurrence of Tumour Lysis Syndrome (TLS) correction of clinically significant dehydration and treatment of high uric acid levels are recommended prior to initiating therapy with TASIGNA (see section 4.8 Adverse effects (undesirable effects)).

TASIGNA may need to be temporarily withheld and/or dose reduced for haematological toxicities (neutropenia, thrombocytopenia) that are not related to underlying leukaemia (Table 1).

Table 1 Dose Adjustments for Neutropenia and Thrombocytopenia

Newly diagnosed CML in chronic phase at 300 mg twice daily Resistant or intolerant CML in chronic Phase CML at 400 mg twice daily	ANC* < 1.0 x 10^9/L and/or platelet counts < 50 x 10^9/L	1. Stop TASIGNA, and monitor blood counts 2. Resume within 2 weeks at prior dose if ANC > 1.0 x 10^9/L and/or platelets > 50 x 10^9/L 3. If blood counts remain low, a dose reduction to 400 mg once daily may be required
Resistant or intolerant CML in accelerated Phase at 400 mg twice daily	ANC* < 0.5 x 10^9/L and/or platelet counts < 10 x 10^9/L	1. Stop TASIGNA, and monitor blood counts 2. Resume within 2 weeks at prior dose if ANC > 1.0 x 10^9/L and/or platelets > 20 x 10^9/L 3. If blood counts remain low, a dose reduction to 400 mg once daily may be required

*ANC = absolute neutrophil count

If clinically significant moderate or severe non-haematological toxicity develops, dosing should be interrupted, and may be resumed at 400 mg once daily once the toxicity has resolved. If the prior dose was 400 mg once daily, treatment should be discontinued. 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 attempted.

Elevated serum lipase: For Grade 3 or 4 lipase elevations, doses should be reduced to 400 mg once daily or interrupted. Serum lipase levels should be tested monthly or as clinically indicated (see section 4.4 Special warnings and precautions for use and section 4.8 Adverse effects (Undesirable effects)).

Elevated bilirubin and hepatic transaminases: For Grade 3 or 4 bilirubin or hepatic transaminase elevations, doses should be reduced to 400 mg once daily or interrupted. Bilirubin and hepatic transaminases levels should be tested monthly or as clinically indicated (see section 4.8 Adverse effects (Undesirable effects)).

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

Method of administration

TASIGNA should be taken twice daily taken approximately 12 hours apart, and must not be taken with food. No food should be consumed for at least 2 hours before and 1 hour after the dose is taken (see section 4.4 Special warnings and precautions for use and section 5.2 Pharmacokinetic properties).

The capsules should be swallowed whole with water. For patients who are unable to swallow capsules, the content of each capsule may be dispersed in one teaspoon of applesauce (pureed

apple) and should be taken immediately. Not more than one teaspoon of applesauce and no food other than applesauce must be used (see section 5.2 Pharmacokinetic properties).

TASIGNA may be given in combination with haematopoietic growth factors such as erythropoietin or G-CSF if clinically indicated. TASIGNA may be given with hydroxyurea or anagrelide if clinically indicated.

Monitoring of response to TASIGNA therapy in Ph+ CML patients should be performed both routinely and when therapy is modified, to identify suboptimal response, loss of response to therapy, poor patient compliance, or possible drug-drug interaction. Results of monitoring should guide appropriate CML management.

4.3 Contraindications

TASIGNA is contraindicated in patients with a known hypersensitivity to nilotinib or to any of the excipients (see section 6.1 List of excipients).

4.4 Special warnings and precautions for use

Myelosuppression

Treatment with TASIGNA is often associated with NCI CTC (National Cancer Institute Common Toxicity Criteria) Grade 3 or 4 thrombocytopenia, neutropenia and anaemia. 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 dose reduction (see section 4.2 Dose and method of administration).

QT Prolongation

In vitro data suggest that nilotinib has the potential to prolong cardiac ventricular repolarisation (QT interval).

In the Phase III study in newly diagnosed Ph+ CML-CP patients the change from baseline in mean time-averaged QTcF interval at steady state observed in the nilotinib 300 mg twice daily group was 6 msec. At the recommended dose of 300 mg twice daily no patient had an absolute QTcF of > 480 milliseconds (ms) and no events of *Torsades de Pointes* were observed.

In the Phase II study in imatinib-resistant and intolerant CML patients in chronic and accelerated phase, treated with nilotinib 400 mg twice daily, the change from baseline in mean time-averaged QTcF interval at steady state was 6 ms and 8 ms, respectively. QTcF of >500 ms was observed in 3 patients (<1% of patients in the Phase II study).

In a healthy volunteer study with exposures that were comparable to the exposures observed in patients, the time-averaged mean placebo-subtracted QTcF change from baseline was 7 msec (CI ± 4 msec). No subject had a QTcF >450 ms. In addition, no clinically relevant arrhythmias were observed during 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 interval. Therefore, co-administration with food must be avoided (see section 4.2 Dose and method of administration) and concomitant use with strong CYP3A4 inhibitors and/or medicinal products with a known potential to prolong QT should be avoided (see section 4.5 Interaction with other medicines and other forms of interactions).

The presence of hypokalaemia and hypomagnesaemia may place patients at risk of developing QT-prolongation (see section 4.2 Dose and method of administration).

TASIGNA should be used with caution in patients who have or who are at significant risk of developing prolongation of QTc, such as those:

- with long QT syndrome,
- with uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia.

In clinical studies, patients with uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina, or clinically significant bradycardia were excluded.

Caution should be exercised in patients with relevant cardiac disorders.

Sudden Death

In clinical trials, uncommon cases (0.1 to 1%) of sudden death have been reported in patients in imatinib-resistant or –intolerant CML patients in chronic and accelerated phase receiving TASIGNA with a past medical history of cardiac disease or significant cardiac risk factors. Comorbidities in addition to the underlying malignancy were also frequently present as were concomitant medications. Ventricular repolarisation abnormalities may have been contributory factors. Based on post-marketing exposure in patient-years, the estimated reporting rate for spontaneous reports of sudden death is 0.02% per patient-year. No cases of sudden deaths have been reported in the newly diagnosed Ph+ CML-CP Phase III study.

Cardiovascular events

Cardiovascular events were reported in the extended follow-up randomized, Phase III nilotinib trial in newly diagnosed CML patients and observed in the post-marketing reports. With a median time on therapy of 60.5 months in the clinical trial, Grade 3 / 4 cardiovascular events included peripheral arterial occlusive disease (1.4% and 1.1% at 300 mg and 400 mg twice a day respectively), ischemic heart disease (2.2% and 6.1% at 300 mg and 400 mg twice a day respectively) and ischemic cerebrovascular events (1.1% and 2.2% at 300 mg and 400 mg twice a day respectively). If acute signs or symptoms of cardiovascular events occur, advise patients to seek immediate medical attention. The cardiovascular status of patients should be evaluated and cardiovascular risk factors should be monitored and actively managed during TASIGNA therapy according to standard guidelines (see section 4.2 Dose and method of administration).

Fluid retention

Severe forms of drug-related fluid retention such as pleural effusion, pulmonary oedema, and pericardial effusion were uncommonly (0.1 to 1%) observed in a Phase III study of newly diagnosed CML patients. Similar events were observed in post-marketing reports. Unexpected, rapid weight gain should be carefully investigated. If signs of severe fluid retention appear

during treatment with nilotinib, the aetiology should be evaluated and patients treated accordingly (see section 4.2 Dose and method of administration).

Hepatitis B reactivation

Reactivation of hepatitis B can occur in patients who are chronic carriers of this virus after receiving a BCR-ABL tyrosine kinase inhibitor (TKI), such as nilotinib. Some cases of hepatitis B reactivation involving drugs of the BCR-ABL TKI class resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome (see section 4.8 Adverse effects (Undesirable effects)).

Patients should be tested for hepatitis B infection before initiating treatment with nilotinib. Patients currently on nilotinib should have baseline testing for hepatitis B 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 hepatitis B serology (including those with active disease) and for patients who test positive for hepatitis B infection during treatment. Carriers of hepatitis B virus who require treatment with nilotinib should be closely monitored for signs and symptoms of active hepatitis B infection throughout therapy and for several months following termination of therapy.

Special monitoring of Ph+ CML-CP patients who have achieved a sustained deep molecular response

Eligibility for Discontinuation of Treatment

Eligible patients who are confirmed to express the typical BCR-ABL transcripts, e13a2/b2a2 or e14a2/b3a2, can be considered for treatment discontinuation. Patients must have typical BCR-ABL transcripts to allow quantitation of BCR-ABL levels, evaluation of the depth of molecular response, and determination of a possible loss of molecular remission after TASIGNA treatment discontinuation.

Monitoring of Patients who have discontinued therapy

Monitoring of BCR-ABL transcript levels in patients eligible for treatment discontinuation must be performed with a quantitative diagnostic test validated to measure molecular response levels with a sensitivity of at least MR 4.5. BCR-ABL transcript levels must be assessed prior to and during treatment discontinuation (see section 4.2 Dose and method of administration and section 5.1 Pharmacodynamic Properties, Clinical Trials).

Loss of MMR or confirmed loss of MR 4.0 (two consecutive measures separated by at least 4 weeks showing loss of MR 4.0) will trigger treatment re-initiation within 4 weeks of when loss of remission is known to have occurred. Molecular relapse can occur during the treatment-free phase, and long-term outcome data are not yet available. It is therefore crucial to perform frequent monitoring of BCR-ABL transcript levels and complete blood count with differential in order to detect possible loss of remission (see section 4.2 Dose and method of administration and section 5.1 Pharmacodynamic Properties, Clinical Trials). For patients who fail to achieve MMR after three months of treatment re-initiation, BCR-ABL kinase domain mutation testing should be performed.

Laboratory tests and monitoring

Blood lipids

In a Phase III study in newly diagnosed CML patients, 1.1% of the patients treated with 400 mg nilotinib twice a day, had a Grade 3/4 elevation in total cholesterol; however, there were

no Grade 3/4 elevations in the 300 mg twice a day dose group. 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 chronic therapy (see section 4.2 Dose and method of administration). If a HMG-CoA reductase inhibitor (a lipid lowering agent) is needed, please refer to section 4.5 Interaction with other medicines and other forms of interactions before starting treatment since certain HMG-CoA reductase inhibitors are metabolized by the CYP3A4 pathway.

Blood glucose

In a Phase III study in newly diagnosed CML patients, 6.9% of the patients treated with 400 mg nilotinib twice a day had a Grade 3/4 elevation in blood glucose; and 7.2% of the patients treated with 300 mg nilotinib twice a day had a Grade 3/4 elevation in blood glucose. It is recommended that the glucose levels should be assessed before initiating treatment with TASIGNA and monitored during treatment as clinically indicated (see section 4.2 Dose and method of administration). If test results warrant therapy, physicians should follow their local standards of practice and treatment guidelines.

Lactose

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

Serum Lipase

Elevation in serum lipase has been observed. 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 exclude pancreatitis (see section 4.2 Dose and method of administration).

Electrolyte Abnormalities

The use of TASIGNA can cause electrolyte imbalances commonly (see section 4.8 Adverse Effects (Undesirable Effects, Metabolism and Nutrition Disorders). Electrolyte abnormalities must be corrected prior to initiating TASIGNA and monitored periodically during therapy.

Hepatotoxicity

Clinical studies showed a risk of increased total bilirubin, ALT and AST levels associated with nilotinib (see section 4.8 Adverse effects (Undesirable effects)).

Total Gastrectomy

The bioavailability of nilotinib might be reduced in patients with total gastrectomy (see section 5 Pharmacological Properties). More frequent follow-up of these patients should be considered.

Tumour Lysis Syndrome

Cases of tumour lysis syndrome have been reported in patients treated with TASIGNA. For monitoring recommendations please refer to section 4.2 Dose and method of administration.

Special Populations

Use in Patients with Hepatic Impairment
Hepatic impairment has a modest effect on the pharmacokinetics of nilotinib. Single dose administration of nilotinib resulted in increases in AUC of 35%, 35% and 19% in subjects with mild, moderate and severe hepatic impairment respectively, compared to a control group of subjects with normal hepatic function. The predicted steady-state C_{max} of nilotinib showed an increase of 29%, 18% and 22% respectively. Pharmacokinetic parameters were subject to high inter-subject variability.

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. Patients with hepatic impairment might therefore have increased exposure to nilotinib and should be treated with caution (see monitoring recommendations in section 4.2 Dose and method of administration).

Use in 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.

Since nilotinib and its metabolites are not renally excreted, a decrease in total body clearance is not anticipated in patients with renal impairment.

Paediatric Use
Safety and efficacy in children and adolescents below the age of 18 has not been established. There have been case reports of growth retardation in paediatric patients treated with TASIGNA.

Use in the Elderly
Approximately 12% and 30% of subjects in the clinical studies (newly diagnosed Ph+ CML-CP and resistant or intolerant Ph+ CML-CP and CML-AP) were 65 years of age or older. No major differences were observed for safety and efficacy in patients ≥ 65 years of age as compared to adults 18 to 65 years.

4.5 Interactions with other medicines and other forms of interactions

The administration of TASIGNA with agents that are strong CYP3A4-inhibitors and drugs that may prolong the QT interval such as anti-arrhythmic medicines should be avoided (see section 4.2 DOSE AND METHOD OF ADMINISTRATION). 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.

Concomitant use of TASIGNA with medicinal products that are potent inducers of CYP3A4 is likely to reduce exposure to nilotinib to a clinically relevant extent. Therefore, in patients receiving TASIGNA, concomitant use of alternative therapeutic agents with less potential for CYP3A4 induction should be selected.

Nilotinib is mainly metabolised 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 Concentration

The bioavailability of nilotinib in healthy subjects was increased 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) (see section 4.2 Dose and method of administration and section 4.4 Special warnings and precautions for use, QT Prolongation). Alternative concomitant medications with no or minimal CYP3A4 inhibition should be considered.

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

Drugs That May Decrease Nilotinib Serum Concentration

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

Inducers of CYP3A4 activity could increase the metabolism of nilotinib and thereby decrease serum concentrations of nilotinib. The concomitant administration of medications that induce CYP3A4 (e.g. phenytoin, rifampicin, carbamazepine, phenobarbital, and St. John's Wort) may reduce exposure to nilotinib. In patients for whom CYP3A4 inducers are indicated, alternative agents with less enzyme induction potential should be considered.

Nilotinib has pH-dependent solubility, with lower solubility at higher pH. In healthy subjects receiving esomeprazole at 40 mg once daily for 5 days, gastric pH was markedly increased, but nilotinib absorption was only decreased modestly (27% decrease in C_{max} and 34% decrease in $AUC_{0-\infty}$). TASIGNA may be used concurrently with esomeprazole or other proton pump inhibitors as needed.

In a healthy subjects study, 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 a H_2 blocker is necessary, it may be administered approximately 10 hours before and approximately 2 hours after the dose of TASIGNA. H_2 blockers which are potent inducers of CYP3A4 should be used with caution.

In the same study as above, administration of an antacid (aluminium 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, an antacid may be administered approximately 2 hours before or approximately 2 hours after the dose of TASIGNA.

Drugs That May Have Their Systemic Concentrations Altered by Nilotinib

Nilotinib is a competitive inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2D6 and UGT1A1 *in vitro*, with Ki value being lowest for CYP2C9 (Ki=0.13 microM).
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) 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 alfentanil, cyclosporine, dihydroergotamine, ergotamine,

fentanyl, astemizole, terfenadine, cisapride, quinidine, pimozide, sirolimus and tacrolimus) when co-administered with nilotinib. Some of these drugs also prolong the QT interval, hence ECG monitoring should also be done if alternative drugs cannot be used.

A single-dose drug-drug interaction study in healthy subjects with warfarin 25 mg, a sensitive CYP2C9 substrate, and nilotinib 800 mg did not result in any changes in warfarin pharmacokinetics (C_{max}, $AUC_{0-\infty}$) or warfarin pharmacodynamics (prothrombin time [PT] and international normalised ratio [INR]). The single-dose drug-drug interaction study suggests that TASIGNA can be used concurrently with warfarin (up to a dose of 25 mg) without increasing the anti-coagulant effect of warfarin. There are no steady-state pharmacokinetic or pharmacodynamic interaction data for co-administration of nilotinib and warfarin. Consequently, monitoring and control of warfarin pharmacodynamic markers (INR or PT) following initiation of nilotinib therapy (at least during the first 2 weeks) is recommended.

Single-dose administration of nilotinib 600 mg with midazolam 4 mg (a CYP3A substrate) to healthy subjects increased midazolam exposure by 30%. There are no steady-state pharmacokinetic interaction data for co-administration of nilotinib and midazolam. Consequently, it is possible that greater exposure to midazolam might occur with steady –state co-administration of nilotinib and midazolam.

Nilotinib is an inhibitor of P-glycoprotein in vitro at clinically relevant concentrations and may potentially influence the absorption/elimination and subsequent serum concentrations of concomitantly-administered drugs that are substrates for this multi-drug efflux pump. Concomitant administration of nilotinib with imatinib, increased the AUC of imatinib by 18% to 39%.

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

Concomitant use of 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, haloperidol, methadone, moxifloxacin, bepridil and pimozide) should be avoided (see section 4.4 Special warnings and precautions for use).

Other Interactions That May Affect Serum Concentrations

The absorption and the bioavailability of nilotinib are increased if it is taken with food, resulting in higher serum concentration (see section 4.2 Dose and method of administration, and section 5.2 Pharmacokinetic Properties).

TASIGNA must not be taken in conjunction with food and should be taken 2 hours after a meal. No food should be consumed for at least one hour after the dose is taken, except apple sauce for patients unable to swallow capsules (see section 4.2 Dose and method of administration). Grapefruit juice and other foods that are known to inhibit CYP3A4 should be avoided at any time.

Solubility of nilotinib decreases with increasing pH and is practically insoluble in buffer solutions of pH 4.5 or higher. Hence, simultaneous treatment with nilotinib and antacids should be avoided. If antacid therapy is needed, the antacid dose should be administered at least 2 hours prior to or 2 hours after TASIGNA dosing.

4.6 Fertility, pregnancy, and lactation

Contraception

Females of reproductive potential must be advised to use effective method of contraception (methods that result in less than 1% pregnancy rates) while receiving TASIGNA and for up to 2 weeks after ending treatment with TASIGNA.

Effects on Fertility

The effect of nilotinib on male and female fertility is not known. In a fertility study in rats, no effects on sperm count/motility were noted in males and no effects on fertility were noted in males or females. The highest tested dose achieved an exposure (based on plasma AUC) of approximately 5 times that expected in humans at the recommended dose. Sexually active male or female patients taking TASIGNA should use highly effective contraception.

Use in Pregnancy (Category D)

TASIGNA can cause foetal harm when administered to a pregnant woman. There are no adequate data on the use of TASIGNA in pregnant women. It should not be used during pregnancy. If the drug is used during pregnancy or if the patient becomes pregnant while taking TASIGNA, the patient must be informed of the potential risk to the foetus.

If a woman who is being treated with TASIGNA is considering pregnancy, treatment discontinuation may be considered based on the eligibility criteria for discontinuing treatment. There is a limited amount of data on pregnancies in patients while attempting treatment-free remission (TFR). If pregnancy is planned during the TFR phase, the patient must be informed of a potential need to re-initiate TASIGNA treatment during pregnancy (see sections 4.2 Dose and method of administration and section 4.4 Special warnings and precautions for use).

In animal studies, nilotinib crossed the placenta and induced embryofoetal toxicity at doses that also showed maternal toxicity. Increased post implantation loss was observed in both the fertility study, which involved treatment of both males and females, and in the embryo toxicity study, which involved treatment of females. Embryo-lethality and foetal effects (mainly decreased foetal weights, and increased skeletal changes) in rats and increased resorption of foetuses and skeletal variations in rabbits were observed in the embryofoetal toxicity studies. Exposure to nilotinib in females at No-Observed-Adverse-Effect-Levels was generally less than or equal to that in humans at 400 mg/b.i.d.

In a pre- and postnatal study, 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). Adverse effects on the reproductive function of pups (lower mating and fertility indices) were also observed at the maternal dose of 60 mg/kg. The No-Observed-Adverse-Effect-Level in maternal animals and offspring was a maternal dose of 20 mg/kg (approximately 1.7 times the plasma AUC in patients at the recommended clinical dose).

Women of childbearing potential must be advised to use highly effective method of contraception while receiving TASIGNA and for up to 2 weeks after ending treatment.

Use in Lactation

It is not known whether nilotinib is excreted in human milk. Studies in animals demonstrate that nilotinib is excreted into milk. Lactating women should therefore not breast-feed while taking TASIGNA and for 2 weeks after the last dose, as a risk to the infant cannot be excluded.

4.7 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 section 4.8 Adverse effects (Undesirable effects)).

4.8 Adverse effects (Undesirable effects)

Summary of the safety profile

The nilotinib safety profile described below 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 listed indications (see Table 7 and section 4.1 Therapeutic indications). Safety information from two TASIGNA treatment discontinuation studies is also provided.

In patients with newly diagnosed Ph+ CML-CP

The data reported below reflect exposure to TASIGNA from a randomised phase III study in patients with newly diagnosed Ph+ CML-CP treated at the recommended dose of 300 mg twice daily (n=279). The median duration of treatment in new patients was 60.5 months (range 0.1 to 70.8 months).

Non-haematologic adverse drug reactions (ADRs) reported with very common frequency (≥10%) were rash, pruritus, headache, nausea, fatigue, alopecia, myalgia, and upper abdominal pain. Most of these ADRs were mild to moderate in severity (Grade 1 or 2). Constipation, diarrhoea, dry skin, muscle spasms, arthralgia, abdominal pain, peripheral oedema, vomiting and asthenia were observed less commonly (<10% and ≥ 5%) and have been of mild to moderate severity, manageable and generally did not require dose reduction. Pleural and pericardial effusions, regardless of causality, occurred in 2% and <1% of patients, respectively, receiving TASIGNA 300 mg twice daily. Gastrointestinal haemorrhage, regardless of causality was reported in 3% of these patients.

The change from baseline in mean time-averaged QTcF interval at steady state in the nilotinib recommended dose of 300 mg twice daily was 6 msec. In the nilotinib 400 mg twice daily group and the imatinib 400 mg once daily group the change from baseline in mean time-averaged QTcF interval at steady state was 6 msec and 3 msec respectively. No patient had an absolute QTcF of >500 msec while on study drug in any of the TASIGNA treatment groups and no events of Torsade de Pointes were observed. QTcF increase from baseline that exceeds 60 msec was observed in 4 patients while on TASIGNA (one in the 300 mg twice daily treatment group and three in the 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 deaths have been reported in any treatment group.

In the nilotinib 300 mg twice daily group, haematologic ADRs include myelosuppression: thrombocytopenia (18%), neutropenia (15%), and anaemia (8%). Biochemistry ADRs include alanine aminotransferase increased (24%), hyperbilirubinaemia (16%), aspartate aminotransferase increased (12%), lipase increased (11%), blood bilirubin increased (10%), hyperglycaemia (4%), hypercholesterolaemia (3%), and hypertriglyceridaemia (<1%). See Table 8 for Grade 3/4 laboratory abnormalities.

Discontinuation due to adverse drug reactions was observed in 10% of patients.

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 (n=321) and CML-AP (n=137) resistant to or intolerant to at least one prior therapy including imatinib in an open-label multicentre study treated at the recommended dose of 400 mg twice daily.

Non-haematologic adverse drug reactions (ADRs) reported with very common frequency (≥10% in the combined CML-CP and CML-AP patient populations) were rash, pruritus, nausea, fatigue, headache, constipation, diarrhoea, 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 ≥ 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. Gastrointestinal and CNS haemorrhage was reported in 1% and <1% of patients, respectively.

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

Haematologic ADRs include myelosuppression: thrombocytopenia (31%), neutropenia (17%), and anaemia (14%). See Table 8 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-haematologic ADRs (excluding laboratory abnormalities) that were reported in at least 5% of the patients in any of the TASIGNA clinical studies that serve as a basis for the listed indications are shown in Table 2. 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 (CIOMS III) convention: very common (≥1/10) or common (≥1/100 to <1/10). The frequency is based on the highest for any TASIGNA group in the two studies, using one decimal precision for percentages.

Comparison of Common Non-Laboratory Adverse Reactions in Clinical Trials

Table 2 Most Frequently Reported Non-haematologic Adverse Drug Reactions (≥5% in any TASIGNA Group)

			Newly Diagnosed Ph+ CML-CP						Resistant or Intolerant Ph+ CML-CP and CML-AP			
			60 months analysis						24 months analysis			
			TASIGNA 300 mg twice daily	TASIGNA 400 mg twice daily	IMATINIB 400 mg once daily	TASIGNA 300 mg twice daily	TASIGNA 400 mg twice daily	IMATINIB 400 mg once daily	TASIGNA 400 mg twice daily			
			ALL GRADES (%)			GRADE 3 or 4 (%)			ALL GRADES (%)	GRADE 3/4 (%)	CML-CP GRADE 3/4 (%)	CML-AP GRADE 3/4 (%)
System Organ Class	**Frequency**	**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	Common	Decreased appetite[1]	4	4	3	0	0	0	8	<1	<1	0
Nervous system disorders	Very common	Headache	16	22	10	2	1	<1	15	1	2	<1
Gastrointestinal disorders	Very common	Nausea	14	21	35	<1	1	<1	20	<1	<1	<1
	Very common	Constipation	10	7	3	0	<1	0	12	<1	<1	0
	Very common	Diarrhoea	9	7	31	<1	0	3	11	2	2	<1

	Very common	Vomiting	6	9	19	0	1	0	10	<1	<1	0
	Very common	Abdominal pain upper	10	9	8	1	0	<1	5	<1	<1	0
	Common	Abdominal pain	6	6	4	0	<1	0	6	<1	<1	<1
	Common	Dyspepsia	5	5	6	0	<1	0	3	0	0	0
Skin and subcutaneous tissue disorders	Very common	Rash	33	39	14	<1	3	2	28	1	2	0
	Very common	Pruritus	18	16	5	<1	<1	0	24	<1	<1	0
	Very common	Alopecia	10	14	6	0	0	0	9	0	0	0
	Very common	Dry Skin	10	12	5	0	0	0	5	0	0	0
	Common	Erythema	3	6	3	0	0	0	5	<1	<1	0
Musculoskeletal and connective tissue disorders	Very common	Myalgia	10	12	13	<1	<1	<1	10	<1	<1	<1
	Very common	Arthralgia	8	10	8	<1	0	<1	7	<1	1	0
	Common	Muscle spasms	9	9	30	0	<1	1	8	<1	<1	0
	Common	Bone pain	4	5	4	0	<1	<1	6	<1	<1	0
	Common	Pain in extremity	5	3	8	<1	<1	<1	5	<1	<1	<1

General disorders and administration site conditions	Very common	Fatigue	12	11	13	0	<1	1	17	1	1	<1
	Common	Asthenia	9	5	9	<1	<1	0	6	0	0	0
	Common	Oedema peripheral	5	7	18	<1	0	0	6	0	0	0

[1] 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.

Additional Data from Clinical Trials

The following adverse drug reactions were reported in patients in the TASIGNA clinical studies which serve as a basis for the listed indications at the recommended doses at the following frequency (very common is ≥ 1/10; common is ≥ 1/100 to < 1/10; uncommon is >1/1,000 to <1/100; single events are captured as frequency not known) Table 3. For laboratory abnormalities, very common events (≥1/10) not included in Table 7 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.

Table 3 Adverse drug reactions reported in clinical studies

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
Frequency not known:	sepsis, subcutaneous abscess, anal abscess, furuncle, tinea pedis, hepatitis B reactivation.
Neoplasms Benign, Malignant and Unspecified	
Common:	skin papilloma
Frequency not known:	oral papilloma, paraproteinemia
Blood and Lymphatic System Disorders	
Common:	leukopenia, eosinophilia, febrile neutropenia, pancytopenia, lymphopenia
Frequency not known:	thrombocythaemia, leukocytosis
Immune System Disorders	
Frequency not known:	hypersensitivity
Endocrine Disorders	
Uncommon:	hyperthyroidism, hypothyroidism
Frequency not known:	hyperparathyroidism secondary, thyroiditis.
Metabolism and Nutrition Disorders	
Very common:	hypophosphataemia (including blood phosphorus decreased)
Common:	electrolyte imbalance (including hyperkalaemia, hypokalaemia, hyponatraemia, hypocalcaemia, hypercalcaemia, hyperphosphataemia, hypomagnesaemia), hyperglycaemia, diabetes mellitus, hypercholesterolaemia, hyperlipidaemia, hypertriglyceridemia
Uncommon:	gout, dehydration, increased appetite, dyslipidemia.
Frequency not known:	hyperuricemia, hypoglycaemia
Psychiatric Disorders	
Common:	depression, insomnia, anxiety
Frequency not known:	disorientation, confusional state, amnesia, dysphoria
Nervous System Disorders	
Common:	dizziness, peripheral neuropathy, hypoaesthesia, paraesthesia
Uncommon:	intracranial haemorrhage, ischemic stroke, transient ischemic attack, cerebral infarction, migraine, loss of consciousness (including syncope), tremor, disturbance in attention, hyperaesthesia

Frequency not known:	cerebrovascular accident, basilar artery stenosis, brain oedema, optic neuritis, lethargy, dysaesthesia, restless legs syndrome

Eye Disorders

Common:	eye haemorrhage, 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 haemorrhage.
Frequency not known:	papilloedema, diplopia, photophobia, eye swelling, blepharitis, eye pain, chorioretinopathy, conjunctivitis allergic, ocular surface disease

Ear and Labyrinth Disorders

Common:	vertigo
Frequency not known:	hearing impaired, ear pain, tinnitus

Cardiac Disorders

Common:	angina pectoris, arrhythmia (including atrioventricular block, cardiac flutter, extrasystoles, atrial fibrillation, tachycardia, bradycardia), palpitations, electrocardiogram QT prolonged
Uncommon:	cardiac failure, myocardial infarction, coronary artery disease, cardiac murmur, pericardial effusion, cardiomegaly, cyanosis.
Frequency not known:	ventricular dysfunction, pericarditis, ejection fraction decrease.

Vascular Disorders

Common:	hypertension, flushing
Uncommon:	hypertensive crisis, peripheral arterial occlusive disease, intermittent claudication, arterial stenosis limb, haematoma, arteriosclerosis
Frequency not known:	shock haemorrhagic, hypotension, thrombosis, peripheral artery stenosis.

Respiratory, Thoracic and Mediastinal Disorders

Common:	dyspnoea, dyspnoea exertional, epistaxis, cough, dysphonia
Uncommon:	pulmonary oedema, pleural effusion, interstitial lung disease, pleuritic pain, pleurisy, pharyngolaryngeal pain, throat irritation
Frequency not known:	pulmonary hypertension, wheezing, oropharyngeal pain

Gastrointestinal Disorders

Common:	pancreatitis, abdominal discomfort, abdominal distension, dyspepsia, dysgeusia, flatulence
Uncommon:	gastrointestinal haemorrhage, melaena, mouth ulceration, gastroesophageal reflux, stomatitis, oesophageal pain, dry mouth, gastritis, sensitivity of teeth
Frequency not known:	gastrointestinal ulcer perforation, retroperitoneal haemorrhage, haematemesis, gastric ulcer, oesophagitis ulcerative, subileus, enterocolitis, haemorrhoids, hiatus hernia, rectal haemorrhage, gingivitis

Hepatobiliary Disorders

Very common:	hyperbilirubinemia (including blood bilirubin increased)
Common:	hepatic function abnormal
Uncommon:	hepatotoxicity, toxic hepatitis, jaundice.
Frequency not known:	cholestasis, 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
Frequency not known:	psoriasis, erythema multiforme, erythema nodosum, skin ulcer, palmar-plantar erthrodysaesthesia syndrome, petechiae, photosensitivity, blister, dermal cyst, sebaceous hyperplasia, skin atrophy, skin discolouration, 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
Frequency not known:	arthritis

Renal and Urinary Disorders

Common:	pollakiuria
Uncommon:	dysuria, micturition urgency, nocturia,
Frequency not known:	renal failure, haematuria, urinary incontinence, chromaturia

Reproductive System and Breast Disorders

Uncommon:	breast pain, gynaecomastia, erectile dysfunction.
Frequency not known:	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 oedema, gravitational oedema, influenza-like illness, chills, feeling body temperature change (including feeling hot, feeling cold)
Frequency not known:	localised oedema

Investigations

Very common:	alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, lipase increased, lipoprotein cholesterol (including low density and high density) increased, total cholesterol increased, blood triglycerides increased.
Common:	haemoglobin decreased, blood amylase increased, gamma-glutamyltransferase increased, blood creatinine phosphokinase increased, blood alkaline phosphatase increased, blood insulin increased, weight decreased, weight increased, globulins decreased
Uncommon:	blood lactate dehydrogenase increased, blood urea increased.
Frequency not known:	troponin increased, blood bilirubin unconjugated increased, blood insulin decreased, insulin C-peptide decreased, blood parathyroid hormone increased

Comparison of Severe Laboratory Abnormalities in Clinical Trials

Table 4 Grade 3/4 Laboratory Abnormalities

	Newly diagnosed Ph+ CML-CP			**Resistant or intolerant Ph+**	
	TASIGNA 300mg twice daily N=279	**TASIGNA 400mg twice daily N=277**	**IMATINIB 400mg once daily N=280**	**CML-CP N=321 %**	**CML-AP N=137 %**
Haematological Parameters					
Myelosuppression					
- Neutropenia	12%	11%	22-%	31%	42%
- Thrombocytopenia	10%	12%	9%	30%	42%
- Anaemia	4%	5%	6%	11%	27%
Biochemistry Parameters					
- Elevated creatinine	0%	0%	<1%	1%	<1%%
- Elevated lipase	9%	10%	4%	18%	18%
- Elevated AST	1%	3%	1%	3%	2%
- Elevated ALT	4%	9%	3%	4%	4%
- Hypophosphatemia	8%	10%	10%	17%	15%
- Elevated Bilirubin (total)	4%	9%	<1%	7%	9%
- Elevated glucose	7%	7%	<1%	12%	6%
- 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

Treatment discontinuation in Ph+ CML-CP patients who have achieved a sustained deep molecular response

After discontinuation of TASIGNA therapy within the framework of attempting treatment-free remission (TFR), patients may experience musculoskeletal symptoms more frequently than before treatment discontinuation, e.g., myalgia, pain in extremity, arthralgia, bone pain, spinal pain, or musculoskeletal pain.

In a Phase II clinical study with newly diagnosed patients with Ph+ CML-CP (N=190), musculoskeletal symptoms within a year of TASIGNA discontinuation were reported in 24.7% vs. 16.3% within the previous year on TASIGNA treatment.

In a Phase II clinical study with patients with Ph+ CML-CP on TASIGNA and previously treated with imatinib (N=126), musculoskeletal symptoms within a year of discontinuation were reported in 42.1% vs. 14.3% within the previous year on TASIGNA treatment.

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

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. 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 nilotinib exposure.

Frequency not known: Tumour lysis syndrome.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

Symptoms and Signs

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.

Treatment

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

For information on the management of overdose contact the Poison Information Centre on 131 126.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Mechanism of action

Nilotinib inhibits BCR-ABL tyrosine kinase activity in the nanomolar range by binding to the ATP-binding site. It also inhibited 32/33 imatinib-resistant mutant forms of BCR-ABL tyrosine kinase that were tested. As a consequence, nilotinib inhibited the proliferation of cell lines carrying these enzymes. Orally- administered nilotinib, as a single agent, was also effective in reducing tumour burden and prolonging survival in a murine model of CML.

Nilotinib had little or no effect against the majority of other protein kinases examined except for the platelet derived growth factor receptor (PDGFRα and β), and stem cell factor receptor (KIT CSF-1R, DDR) kinases which it inhibited at concentrations within the range achieved following oral administration at therapeutic doses recommended for the treatment of CML.

Clinical Trials

Newly Diagnosed Philadelphia Chromosome Positive Chronic Myeloid Leukaemia in Chronic Phase (Ph+ CML-CP)

An open label, multicentre, randomised Phase III study 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, or a maximum of two weeks of imatinib in emergent cases. In addition, patients were stratified according to Sokal risk score at time of diagnosis.

Efficacy was based on a total of 846 patients (283 patients in the imatinib 400 mg once daily group, 282 patients in the nilotinib 300 mg twice daily group, 281 patients in the nilotinib 400 mg twice daily group).

Baseline characteristics were well balanced between the three groups. Median age was 46 years in the imatinib group and 47 years in both nilotinib groups, with 12.4%, 12.8% and 10.0% were ≥65 years of age in imatinib, nilotinib 300 mg twice daily and nilotinib 400 mg twice daily treatment groups, respectively. There were slightly more male than female patients in all groups (55.8%, 56.0% and 62.3% in imatinib, nilotinib 300 mg twice daily and nilotinib 400 mg twice daily, respectively). More than 60% of all patients were Caucasian, and 25% were Asian.

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 was 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 and 773 mg/day in the nilotinib 400 mg twice daily group. This study is on-going.

Major molecular response (MMR):
The primary efficacy variable was MMR at 12 months after the start of study medication. MMR was defined as ≤ 0.1% BCR-ABL/ABL % by international scale measured by RQ-PCR, which corresponds to a ≥ 3 log reduction of BCR-ABL transcript from standardised baseline.

The 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. The rate of MMR at 12 months, was also statistically significantly higher in the nilotinib 400 mg twice daily group compared to the imatinib 400 mg once daily group, Table 1.

In the nilotinib recommended dose of 300 mg twice daily, the rate of MMR at 3, 6, 9 and 12 months were 8.9%, 33.0%, 43.3% and 44.3%. In the nilotinib 400 mg twice daily group, the rate of MMR at 3, 6, 9 and 12 months were 5.0%, 29.5%, 38.1% and 42.7%. In the imatinib 400 mg once daily group, the rate of MMR at 3, 6, 9 and 12 months were 0.7%, 12.0%, 18.0% and 22.3%.

The MMR rate at 12, 24, 36, 48 and 60 months is presented in Table 5.

Table 5 MMR rate

	TASIGNA 300 mg twice daily N=282 n (%)	**TASIGNA 400 mg twice daily N=281 n (%)**	**Glivec 400 mg once daily N=283 n (%)**
MMR at 12 months	125(44.3)	120(42.7)	63(22.3)
95% CI for response rate	[38.4, 50.3]	[36.8, 48.7]	[17.6, 27.6]
MMR at 24 months	174 (61.7) [1]	166 (59.1) [1]	106 (37.5)
95% CI for response	[55.8,67.4]	[53.1,64.9]	[31.8,43.4]
MMR at 36 months[2]	165 (58.5)[1]	161 (57.3) [1]	109 (38.5)
95% CI for response	[52.5,64.3]	[51.3,63.2]	[32.8,44.5]
MMR at 48 months[3]	169 (59.9) [1]	155 (55.2)	124 (43.8)
95% CI for response	[54.0, 65.7]	[49.1, 61.1]	[38.0, 49.8]
MMR at 60 months[4]	177 (62.8)	172 (61.2)	139 (49.1)
95% CI for response	[56.8, 68.4]	[55.2, 66.9]	[43.2, 55.1]

[1] CMH test p-value for response rate (vs. Imatinib 400 mg) <0.0001

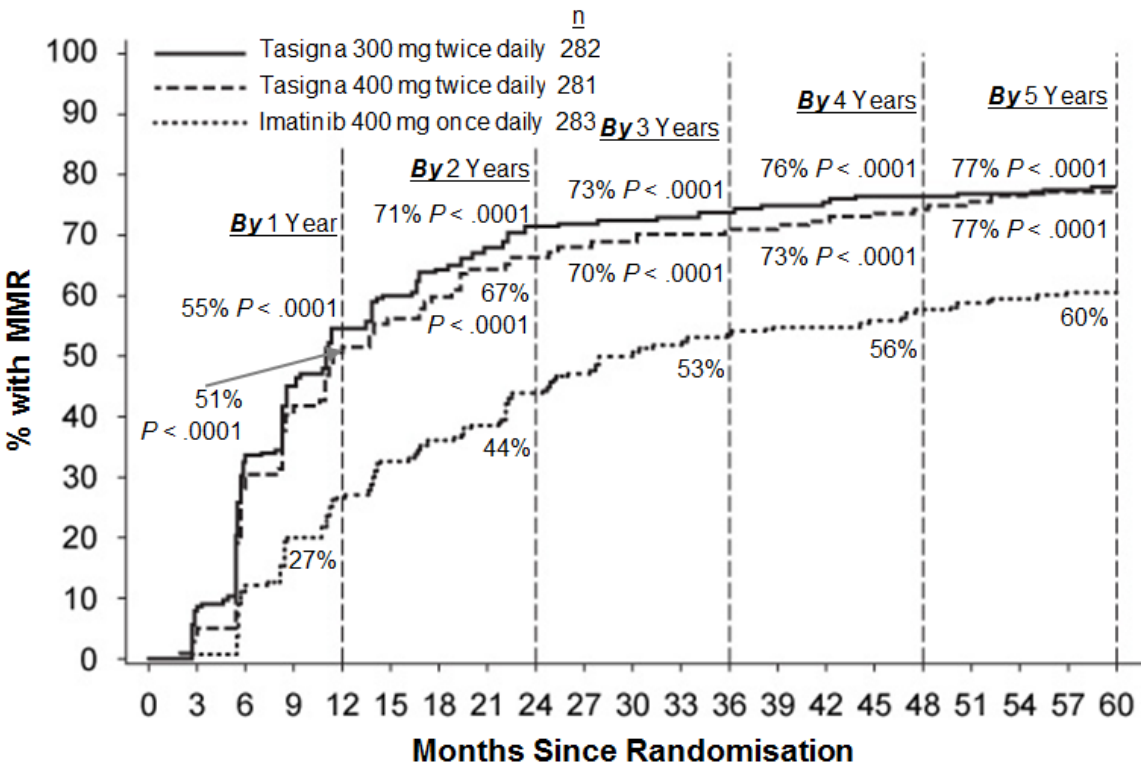
[2] Only patients who were in MMR at a specific time point are included as responders for that time point. A total of 199 (35.2%) of all missing/unevaluable PCR assessments (n=17), atypical transcripts at baseline (n=7), or discontinuation prior to the 36-month time patients were not evaluable for MMR at 36 months (87 in the nilotinib 300 mg BID group and 112 in the imatinib group) due to point (n=175).

[3] Only patients who were in MMR at a specific time point are included as responders for that time point. 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/unevaluable PCR assessments (n=18), atypical transcripts at baseline (n=8), or discontinuation prior to the 48-month time point (n=279).

[4] Only patients who were in MMR at a specific time point are included as responders for that time point. 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/unevaluable 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 1).

Figure 1 Cumulative Incidence of MMR



For all Sokal risk groups, the MMR rates at all time points remained consistently higher in the two nilotinib groups than in the imatinib group.

Based on the Kaplan-Meier analyses of time to first MMR among all patients are graphically displayed in Figure 1. The probability of achieving MMR at different time points were higher in both nilotinib groups compared to the imatinib group (HR=2.20- and stratified log-rank p<0.0001 between nilotinib 300 mg twice daily and imatinib, HR=1.90-- and stratified log-rank p<0.0001 between nilotinib 400 mg twice daily and imatinib). 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 26 and by different time-points are presented in Figure 2 and 3. Molecular response of ≤ 0.01% and ≤ 0.0032% by IS corresponds to a ≥ 4 log reduction and ≥ 4.5 log reduction, respectively, of BCR-ABL transcripts from a standardized baseline.

Table 6 Proportions of patients who had molecular response of ≤ 0.01% (4 log reduction and ≤ 0.0032% (4.5 log reduction)

	TASIGNA 300 mg twice daily N=282 (%)		TASIGNA 400 mg twice daily N=281 (%)		Imatinib 400 mg once daily N=283 (%)	
	≤ 0.01%	≤ 0.0032%	≤ 0.01%	≤ 0.0032%	≤ 0.01%	≤ 0.0032%
At 12 months	11.7	4.3	8.5	4.6	3.9	0.4
At 24 months	24.5	12.4	22.1	7.8	10.2	2.8
At 36 months	29.4	13.8	23.8	12.1	14.1	8.1
At 48 months	33.0	16.3	29.9	17.1	19.8	10.2
At 60 months	47.9	32.3	43.4	29.5	31.1	19.8

Figure 2 Cumulative incidence of molecular response of ≤ 0.01% (4-log reduction)

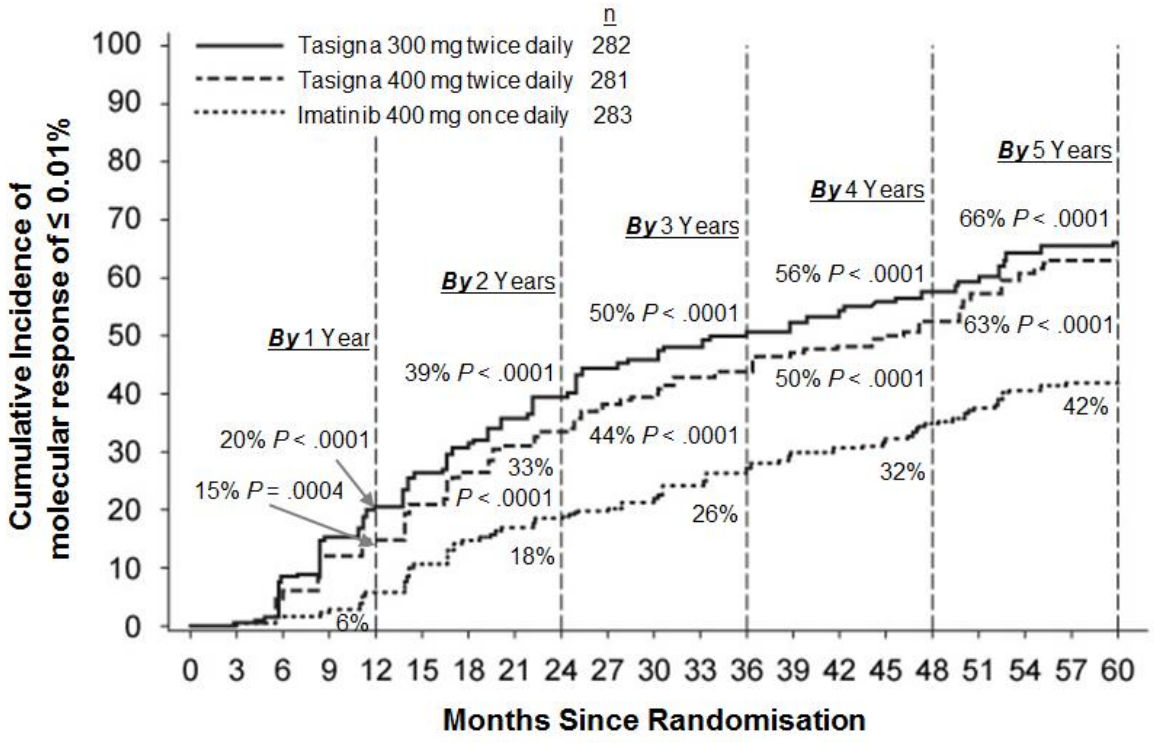
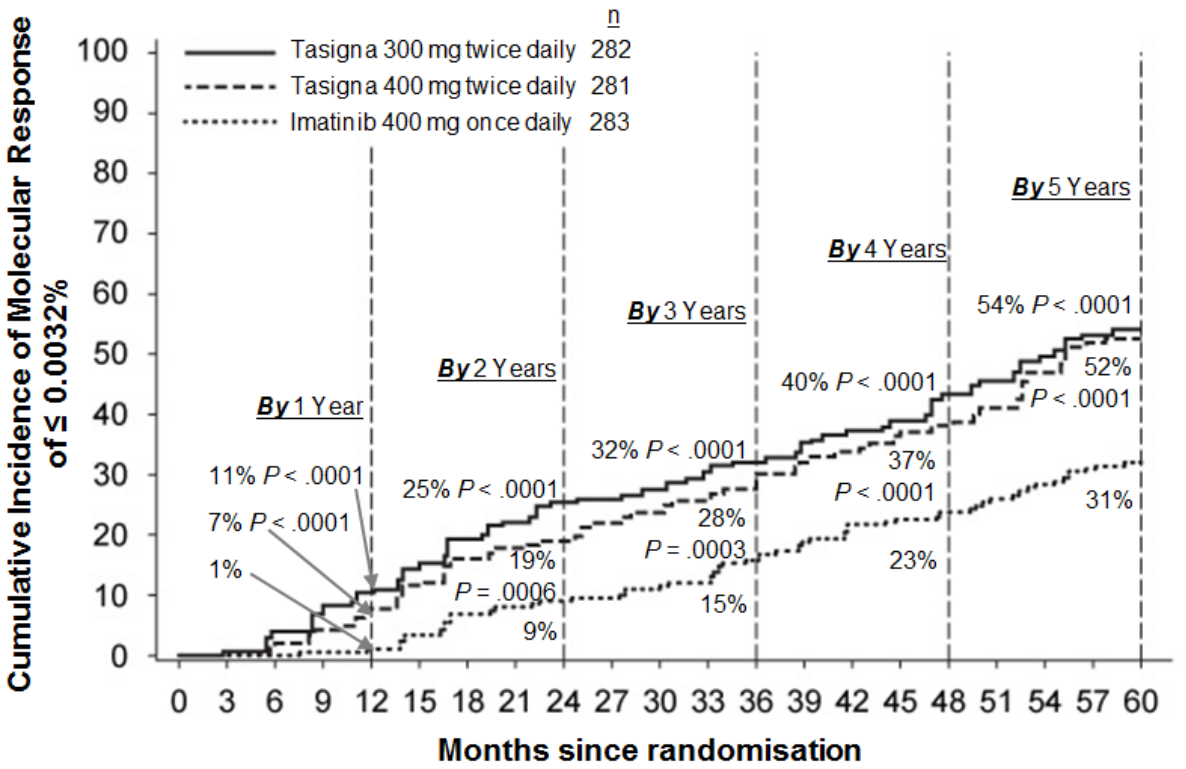


Figure 3 Cumulative incidence of molecular response of ≤ 0.0032% (4.5 log reduction)



Duration of MMR:
Based on Kaplan-Meier estimates of the duration of first MMR, the proportions of patients who were maintaining response after 60 months among patients who achieved MMR were 93.4% (95% CI: 89.9% – 96.9%) in the nilotinib 300 mg twice daily group, 92.0% (95% CI: 88.2% - 95.8%) in the nilotinib 400 mg twice daily group and 89.1% (95% CI: 84.2% - 94.0%) in the imatinib 400 mg once daily group.

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 both the nilotinib 300 mg twice daily and 400 mg twice daily groups compared to imatinib 400 mg once daily group, Table 7.

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

Table 7 CCyR rate

	TASIGNA 300 mg twice daily N=282 n (%)	**TASIGNA 400 mg twice daily N=281 n (%)**	**Imatinib 400 mg once daily N=283 n (%)**
By 12 months			
Complete Cytogenetic Response	226 (80.1)	219 (77.9)	184 (65.0)
95% CI for response	[75.0,84.6]	[72.6,82.6]	[59.2,70.6]
CMH test p-value for response rate (vs. imatinib 400 mg)	<0.0001	0.0005	
By 24 months			
Complete Cytogenetic Response	245 (86.9%)	238 (84.7%)	218 (77.0%)
95% CI for response	[82.4, 90.6]	[79.9, 88.7]	[71.7, 81.8]
CMH test p-value for response rate (vs imatinib 400 mg)	0.0018	0.0160	

Duration of CCyR
Based on Kaplan-Meier estimates, the proportions of patients who were maintaining response after 60 months among patients who achieved CCyR were 99.1% (95% CI: 97.9% – 100%) in the nilotinib 300 mg twice daily group, 98.6% (95% CI: 97.1% - 100%) in the nilotinib 400 mg twice daily group and 97.5% (95% CI: 95.4% - 99.7%) in the imatinib 400 mg once daily group.

Progression to AP/BC on treatment
Progression to AP/BC on treatment is defined as the time from the date of randomization to the first documented disease progression to AP/BC or CML-related death. Overall by the cut-off date, 17 patients progressed to AP or BC on treatment (2 in the nilotinib 300 mg twice daily group, 3 in the nilotinib 400 mg twice daily group and 12 in the imatinib 400 mg once daily group). The estimated rates of patients free from progression to AP or BC at 60 months were 99.3%, 98.7% and 95.2%, respectively (HR=0.1599 and stratified log-rank p=0.0059 between nilotinib 300 mg BID and imatinib, HR=0.2457 and stratified log-rank p=0.0185 between nilotinib 400 mg BID and imatinib).

Including clonal evolution as a criterion for progression, a total of 24 patients progressed to AP or BC on treatment by the cut-off date (2 in the nilotinib 300 mg twice daily group, 5 in the nilotinib 400 mg twice daily group and 17 in the imatinib 400 mg once daily group). The estimated rates of patients free from progression to AP or BC including clonal evolution at 60 months were 98.7%, 97.9% and 93.2%, respectively (HR=0.1626 and stratified log-rank p=0.0009 between nilotinib 300 mg BID and imatinib, HR = 0.2848 and stratified log-rank p=0.0085 between nilotinib 400 mg BID and imatinib).

No new progression to AP/BC were reported since the 2-year analysis.

Overall Survival (OS)
A total of 50 patients died during 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). Twenty-six (26) of these 50 deaths were related to CML (6 in the nilotinib 300 mg twice daily group, 4 in the nilotinib 400 mg twice daily group and 16 in the imatinib 400 mg once daily group). The estimated rates of patients alive at 60 months were 93.7%, 96.2% and 91.7%, respectively (HR=0.8026 and stratified log-rank p = 0.4881 between nilotinib 300 mg twice daily and imatinib, HR=0.4395 and stratified log-rank p = 0.0266 between nilotinib 400 mg twice daily and imatinib). Considering only CML-related deaths as events, the estimated rates of OS at 60 months were 97.7%, 98.5% and 93.8%, respectively (HR=0.3673 and stratified log-rank p = 0.0292 between nilotinib 300 mg twice daily and imatinib, HR=0.2411 and stratified log-rank p = 0.0057 between nilotinib 400 mg twice daily and imatinib).

Resistant or Intolerant Ph+ CML
An open label uncontrolled multicentre Phase II study was conducted to determine the efficacy of TASIGNA (400 mg twice daily) in patients with imatinib resistant or intolerant CML with separate treatment arms for chronic and accelerated phase disease. The study is ongoing. Efficacy was based on 321 chronic phase (CP) patients and 137 accelerated phase (AP) patients enrolled. Median age was 58 years (range 21 – 85 years), with 31% of patients ≥ 65 years of age. There were 48% females and 52% males; 89% caucasian, 4% asian and 5% black patients. TASIGNA was administered on a continuous basis (400 mg twice daily at least 2 hours after a meal and with no food for at least one hour after administration) unless there was evidence of inadequate response or disease progression where dose escalation to 600 mg twice daily was allowed.

Table 8 Duration of Exposure with TASIGNA®

	Chronic Phase N = 321	**Accelerated Phase N = 137**
Median duration of therapy in months (25th-75th percentiles)	18.4 (6.4-28.0)	8.7 (3.8-19.6)

The patients' CML disease history is given in Table 9. Resistance to imatinib included failure to achieve a complete haematological 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 haematological response. Imatinib intolerance included patients who discontinued imatinib because of toxicity and who were not in major cytogenetic response at time of study entry.

The majority of patients had a long history of CML that included extensive prior treatment with other antineoplastic agents including imatinib, hydroxyurea, interferon, and some who had even failed stem cell transplant (Table 6). The median highest prior imatinib dose had been 600 mg/day for both CP and AP patients, and the highest prior imatinib dose was >600 mg/day in 74% of all patients with 40% of patients receiving imatinib doses >800 mg/day.

Table 9 CML Disease History Characteristics

	Chronic Phase (n = 321)	**Accelerated Phase (n = 137)**
Median time since diagnosis in months (range)	58 (5-275)	71 (2-298)
Imatinib		
Resistant	226 (70%)	109 (80%)
Intolerant without MCyR	95 (30%)	27 (20%)
Median time of imatinib treatment in months (25th-75th percentiles)	32 (17-49)	28 (14-49)
Prior Hydroxyurea	83%	91%
Prior Interferon	58%	50%
Prior non-drug organ transplant	7%	8%

MCyR = major cytogenetic response

The primary endpoint in the CP patients was major cytogenetic response (MCyR), defined as elimination (CCyR, complete cytogenetic response) or significant reduction to <35% Ph+ metaphases (partial cytogenetic response) of Ph+ haematopoietic cells. Complete haematological response (CHR) in CP patients was evaluated as a secondary endpoint. For efficacy assessment, patients needed to have completed 6 months treatment or discontinued the study.

The primary endpoint in the AP patients was overall confirmed haematological response (HR), defined in this trial as either a complete haematological response, no evidence of leukaemia or return to chronic phase. For efficacy assessment, patients needed to have completed 4 months treatment, discontinued the study or achieved a complete haematological response.

Complete Haematologic Response (CHR) criteria:

Chronic CML: White Blood Cell Count < 10 x 10^9 /L, no blasts or promyelocytes in peripheral blood, platelets < 450 x 10^9/L, < 5% myelocytes plus metamyelocytes in peripheral blood, basophils < 5% in bone marrow and peripheral blood, and no extramedullary involvement.

Accelerated CML: Myeloblasts < 5% in bone marrow & 0 % in peripheral blood, Absolute Neutrophil Count ≥ 1.5 x 10^9/L, platelets ≥ 100 x 10^9/L, basophils < 5% in bone marrow and peripheral blood and no extramedullary involvement.

The rates of response for the Chronic Phase (CP) and Accelerated Phase (AP) treatment arms are reported in Table 10.

Table 10 Response in CML
Interim results of the intent-to-treat (ITT) analysis of patients with at least 24 months follow up

(Best Response Rate)	Chronic Phase			Accelerated Phase
	Intolerant (n=95)	Resistant (n=226)	Total (n=321)	Total (n=137)
Haematologic Response (%)				
Overall (95%CI)	-	-	-	55 (47-64)
Complete	90 (79-97)	72 (64-79)	76[1] (70-82)	31
NEL	-	-	-	12
Return to chronic phase	-		-	12
Median time to HR (months)	-	-	1.0	1.0
Median duration of HR (months)	-	-	Not reached	21.5
Cytogenetic Response (%)				
Major (95%CI)	66 (56-76)	56 (49-63)	59 (54-65)	32 (24-41)
Complete	51	41	44	21
Partial	16	15	15	11
Median time to MCyR (months)	-	-	2.8	2.8
Median duration of MCyR (months)	-	-	Not reached	Not reached
Overall survival				
24 month overall survival rate (%) (Kaplan-Meier estimate)	-	-	87%	70%

NEL = no evidence of leukaemia/ marrow response; MCyR = major cytogenetic response; CHR = Complete Haematologic Response; HR = Haematologic Response

[1] This result is for patients who had not achieved a complete haematological response at study entry (n = 207)

TASIGNA was investigated separately in CML-CP and CML-AP patients with extensive previous treatment including a tyrosine kinase inhibitor in addition to imatinib. The majority (83% of CML-CP patients and 85% of CML-AP patients) were imatinib-resistant and the remainder imatinib-intolerant. In the 22 CML-CP patients, (32%) achieved a MCyR with TASIGNA. In those without a CHR at baseline (n=16), (50%) achieved a CHR. In the 11 CML-AP patients, (36%) achieved a confirmed HR and one (9%) a MCyR.

Treatment discontinuation in newly diagnosed Ph+ CML-CP patients who have achieved a sustained deep molecular response

In an open-label, multicentre, single-arm study, 215 adult patients with Ph+ CML-CP treated with TASIGNA in first-line for ≥2 years who achieved MR4.5 as measured with the MolecularMD MRDx™ BCR-ABL Test were enrolled to continue TASIGNA treatment for an additional 52 weeks (TASIGNA consolidation phase). The study enrolled patient with typical BCR-ABL transcripts [b3a2 (e14a2) and/or b2a2 (e13a2)] at the time of CML-CP diagnosis i.e. prior to first start of TKI treatment which were amendable to standardized reverse transcriptase PCR. Of the 215 patients, 190 patients (88.4%) entered the Treatment-free Remission (TFR) phase after achieving a sustained deep molecular response during the consolidation phase, defined by the following criteria:

- The 4 last quarterly assessments (taken every 12 weeks) were at least MR4 (BCR-ABL / ABL ≤0.01% IS), and maintained for 1 year
- The last assessment being MR4.5 (BCR-ABL / ABL ≤0.0032% IS)
- No more than two assessments falling between MR4 and MR4.5 (0.0032% IS <BCR-ABL / ABL ≤0.01% IS).

In the set of patients who entered the TFR phase, the median age was 55 years. The proportion of female patients was 49.5%, and 21.1% of the patients were ≥65 years of age. The median actual dose intensity during the 52-week TASIGNA consolidation phase was 600 mg/day.

BCR-ABL levels were monitored every 4 weeks during the first 48 weeks of the TFR phase. Monitoring frequency was intensified to every 2 weeks upon the loss of MR4.0. Biweekly monitoring ended at one of the following time points:

- Loss of MMR requiring patient to re-initiate TASIGNA treatment
- When the BCR-ABL levels returned to a range between MR4.0 and MR4.5
- When the BCR-ABL levels remained lower than MMR for 4 consecutive measurements (8 weeks from initial loss of MR4.0).

Any patient with loss of MMR during the TFR phase re-initiated TASIGNA treatment at 300 mg twice daily or at a reduced dose level of 400 mg once daily if required from the perspective of tolerance, within 5 weeks after the collection date of the blood sample demonstrating loss of MMR. Patients who required re-initiation of TASIGNA treatment were monitored for BCR-ABL levels every 4 weeks for the first 24 weeks and then every 12 weeks thereafter in patients who regained MMR.

The primary endpoint was the percentage of patients who were in MMR at 48 weeks after starting the TFR phase (considering any patient who required re-initiation of treatment as non-responder). Of the 190 patients who entered the TFR phase, 98 patients (51.6% [95% CI: 44.2, 58.9]) were in MMR in the TFR phase at 48 weeks.

The pre-specified primary endpoint was that the lower limit of the 95% CI for the MMR rate at 48 weeks after starting the TFR phase should be greater than 50%. Thus the primary endpoint of the study was not met.

Eighty-eight patients (46.3%) discontinued from the TFR phase due to loss of MMR, and 1 (0.5%), 1 (0.5%), and 3 patients (1.6%) due to death from unknown cause, physician decision, and subject decision, respectively. Among the 88 patients who discontinued the TFR phase

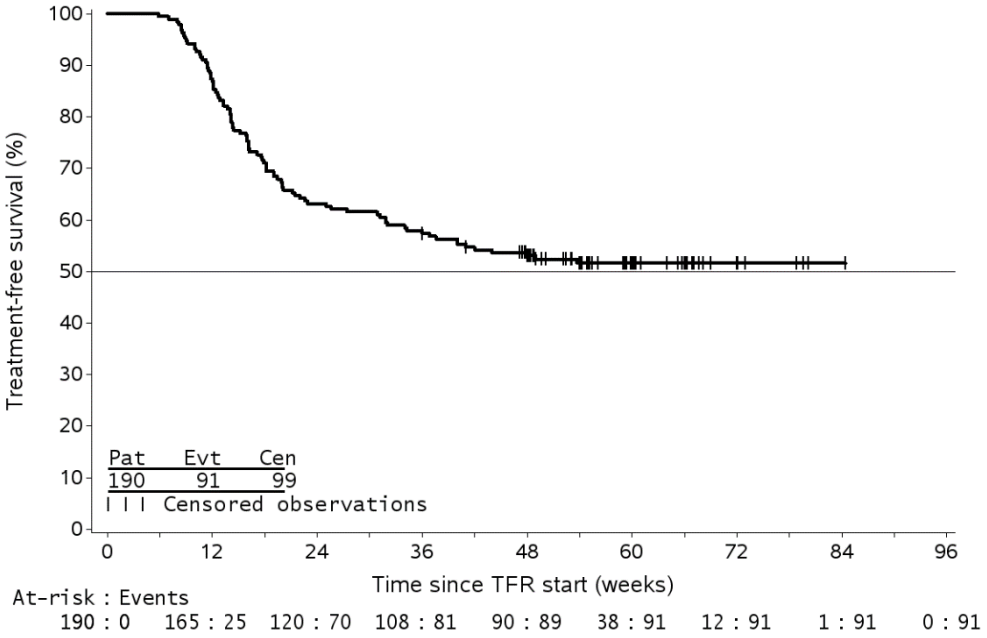
due to loss of MMR, 86 patients restarted TASIGNA treatment and 2 patients permanently discontinued from the study.

Of the 86 patients who restarted treatment due to loss of MMR in the TFR phase, 85 patients (98.8%) regained MMR, (one patient discontinued study permanently due to subject decision) and 76 patients (88.4%) regained MR4.5 by the time of the cut-off date. Ten of the 86 patients (11.6%) did not regain MR4.5 by the time of cut-off and the long term clinical consequences of this loss of deep molecular response are unknown.

The Kaplan-Meier (KM) estimated median time on TASIGNA to regain MMR and MR4.5 was 7.9 weeks (95% CI: 5.1, 8.0) and 13.1 weeks (95% CI: 12.3, 15.7), respectively. The KM estimated MMR rate at 24 weeks of re-initiation was 98.8% (95% CI: 94.2, 99.9). The KM estimated MR4.5 rate at 24 weeks of re-initiation was 90.9% (95% CI: 83.2, 96.0).

Among the 190 patients in the TFR phase, 99 patients (52.1%) did not have a treatment-free survival (TFS) event on or before the 48 month cut-off date, and were censored at the date of their last assessment prior to cut-off. The KM estimate of median TFS has not yet been reached (Figure 4)

Figure 4 **Kaplan-Meier estimate of treatment-free survival after start of TFR (Full Analysis Set)**



Treatment discontinuation in Ph+ CML-CP patients who have achieved a sustained deep molecular response on TASIGNA following prior imatinib therapy

In an open-label, multicentre, single-arm study, 163 adult patients with Ph+ CML-CP taking tyrosine kinase inhibitors (TKIs) for ≥3 years (imatinib as initial TKI therapy for more than 4 weeks without documented MR4.5 on imatinib at the time of switch to TASIGNA, then switched to TASIGNA for at least two years), and who achieved MR4.5 on TASIGNA treatment as measured with the MolecularMD MRDx™ BCR-ABL Test were enrolled to continue TASIGNA treatment for an additional 52 weeks (TASIGNA consolidation phase). Of the 163 patients, 126 patients (77.3%) entered the TFR phase after achieving a sustained deep molecular response during the consolidation phase, defined by the following criterion:

- The 4 last quarterly assessments (taken every 12 weeks) showed no confirmed loss of MR4.5 (BCR-ABL/ABL ≤ 0.0032% IS) during 1 year.

The median age of the patients who entered the TFR phase was 56 years. The proportion of female patients was 55.6%, and 27.8% of the patients were ≥65 years of age. The median actual dose intensity during the 52-week TASIGNA consolidation phase was 771.8 mg/day with 52.4% and 29.4% of patients receiving a daily TASIGNA dose of 800 mg and 600 mg just before entry into the TFR phase, respectively.

Patients who entered the TFR phase but experienced two consecutive measurements of BCR-ABL/ABL >0.01% IS were considered having a confirmed loss of MR4.0, triggering re-initiation of TASIGNA treatment. Patients with loss of MMR in the TFR phase immediately restarted TASIGNA treatment without confirmation. All patients who restarted TASIGNA therapy had BCR-ABL transcript levels monitored every 4 weeks for the first 24 weeks, then once every 12 weeks.

The primary endpoint was defined as the proportion of patients without confirmed loss of MR4.0 or loss of MMR within 48 weeks following discontinuation of TASIGNA therapy. Of the 126 patients who entered the TFR phase, 73 patients (57.9%, [95% CI: 48.8, 66.7]) had no loss of MMR, no confirmed loss of MR4.0, and no re-initiation of TASIGNA therapy within 48 weeks after the start of the TFR phase.

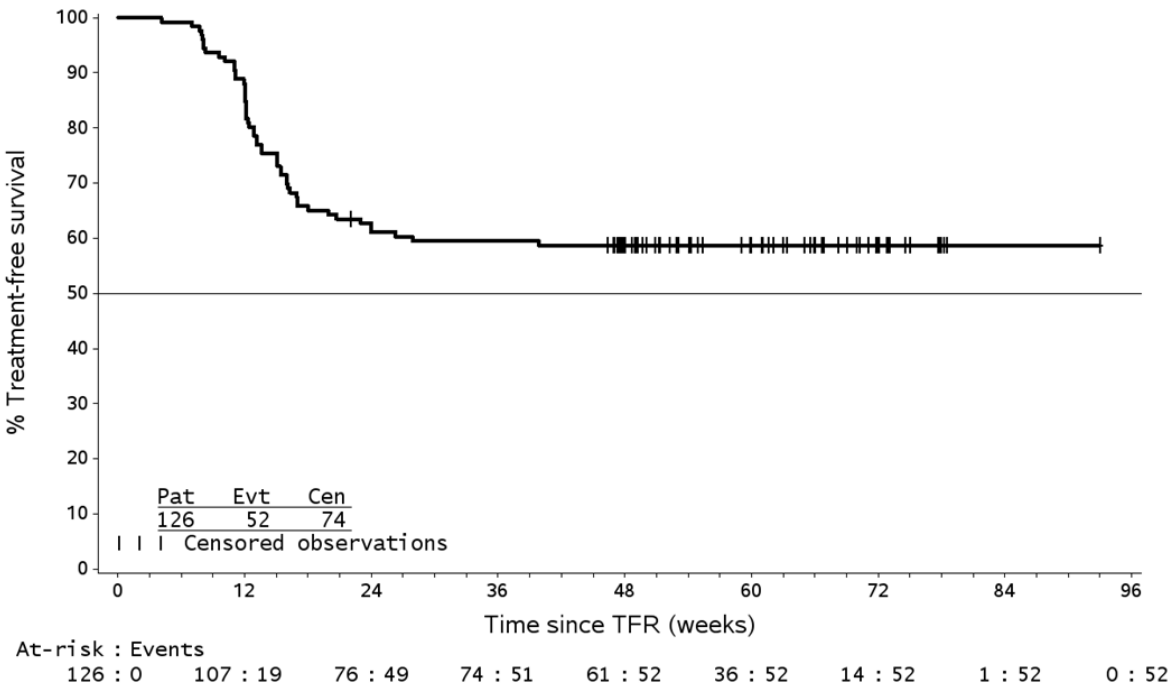
Among the 53 patients who discontinued from the TFR phase due to confirmed loss of MR4.0 or loss of MMR, 51 patients restarted TASIGNA therapy and 2 patients permanently discontinued from the study. Of the 51 patients who restarted TASIGNA treatment due to confirmed loss of MR4.0 or loss of MMR in the TFR phase, 48 patients (94.1%) regained MR4.0 and 3 patients (5.9%) did not regain MR4.0. Forty-seven patients (92.2%) regained MR4.5 and 4 patients (7.8%) did not regain MR4.5 by the time of the cut-off date.

Four of 51 patients (7.8%) did not regain MR4.5 by the time of cut-off and the long term clinical consequences of this loss of deep molecular response are unknown.

The Kaplan-Meier (KM) estimated median time on TASIGNA to regain MR4.0 and MR4.5 was 12.0 weeks (95% CI: 8.3, 12.7) and 13.1 weeks (95% CI: 12.4, 16.1), respectively. The KM estimated rate of MR4.0 at 48 weeks of re-initiation was 100.0%. (95% CI: not estimated). The KM estimated rate of MR4.5 at 48 weeks of re-initiation was 94.8% (95% CI: 85.1, 99.0).

Among the 126 patients in the TFR phase, 74 patients (58.7%) did not have a treatment-free survival (TFS) event on or before the 48-month cut-off date, and were censored at the date of their last assessment prior to cut-off. The other 52 patients had a TFS event (18 patients had confirmed loss of MR4.0, and 34 patients lost MMR). The median TFS has not yet been reached (Figure 5).

Figure 5 **Kaplan-Meier estimate of treatment-free survival after start of TFR (Full Analysis Set)**



5.2 Pharmacokinetic Properties

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. As compared to an oral drink solution (pH of 1.2 to 1.3), relative bioavailability of nilotinib capsule is approximately 50%.

In healthy volunteers, C_{max} 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 section 4.2 Dose and method of administration). Nilotinib absorption (relative bioavailability) might be reduced by approximately 48% and 22% in patients with total gastrectomy and partial gastrectomy, respectively.

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:

The blood-to-serum ratio of nilotinib is 0.68. Serum 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.

Of the nilotinib metabolites, the pyrimidine-N-oxide metabolite (BEJ866) has been found to possess inhibitory activity against the Bcr-Abl kinase in transfected murine hematopoietic cells, albeit at concentrations much higher than those required by the parent drug, nilotinib. The mean serum exposure of BEJ866 is 1.0% of the exposure 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 faeces (93% of the dose). Parent drug accounted for 69% of the dose.

Other information:
Steady-state nilotinib exposure was dose-dependent with less than dose-proportional increases in systemic exposure at dose levels higher than 400 mg given as once daily dosing. Daily serum exposure to nilotinib of 400 mg twice-daily dosing at steady state was 35% higher than with 800 mg once-daily dosing. 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. The average nilotinib trough and peak concentrations over 12 months 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. The apparent elimination half-life estimated from the multiple dose pharmacokinetics with daily dosing was approximately 17 hours. Inter-patient variability in nilotinib pharmacokinetics was moderate to high.

Pharmacokinetics in special patient groups:

Age, body weight, or ethnic origin do not 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.

5.3 Preclinical safety data

Genotoxicity

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

Carcinogenicity
In a 2 year carcinogenicity study, rats were administered oral doses of nilotinib up to 40 mg/kg/day. Exposures at the highest dose level were approximately 2 to 3 times the human steady state exposure (based on AUC) to nilotinib at the dose of 800 mg/day. The major target organ for drug-related lesions was the uterus (dilatation, vascular ectasia, hyperplasia endothelial cell, inflammation and/or epithelial hyperplasia). There was a dose-related increase in the severity of uterine squamous metaplasia and a non-statistically significant increase in the incidence of uterine squamous cell carcinoma at the highest dose. The clinical relevance of these findings is uncertain.

In a 26-week TgHras2 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/day,

representing approximately 24 to 34 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 11 to 18 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) the thymus (increased incidence and/or severity of decreased lymphocytes), kidneys (tubular degeneration/regeneration), and epididymis (inflammation and hypospermia).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content: lactose, crospovidone, poloxamer, silica - colloidal anhydrous, magnesium stearate.

Capsule: gelatin, titanium dioxide, iron oxide yellow, iron oxide red, Opacode S-1-277002 Black (150 mg printing ink), TekPrint SW-1102 Red Ink (200 mg printing ink).

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

TASIGNA is available in 28's (weekly), 40's, 42's and 112's and 120's (monthly) packs. The weekly pack contains 2 calendar cards (daytime and night time) of 14 capsules or a carton of 28 capsules.

The monthly pack consists of 4 packs of 28 capsules or 3 packs of 40 capsules.

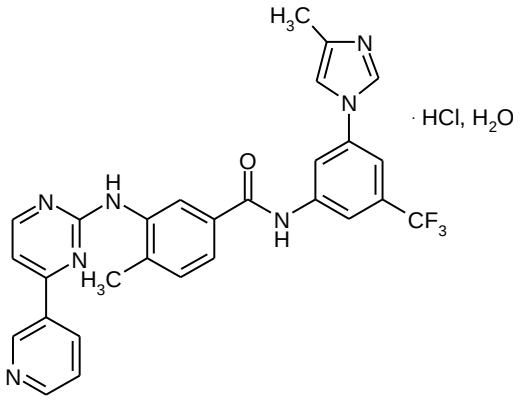
6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physiochemical properties

Chemical name (CAS):	4-Methyl-N-[3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl) phenyl]-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-benzamide, monohydrochloride, monohydrate
Molecular formula:	$C_{28}H_{22}F_3N_7O.HCl.H_2O$
CAS number:	Free base - 641571-10-0
Molecular weight:	583.99 (as monohydrate)

Structural formula:



The solubility of nilotinib in aqueous solutions strongly decreases with increasing pH, and it is practically insoluble in buffer solutions of pH 4.5 and higher pH values. It is very soluble in dimethyl sulfoxide, sparingly soluble in ethanol and methanol, very slightly soluble in acetonitrile and n-octanol.

7. POISON SCHEDULE (POISON STANDARD)

Prescription Only Medicine (Schedule 4)

8. SPONSOR

Novartis Pharmaceuticals Australia Pty Ltd
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Macquarie Park NSW 2113
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Web site: www.novartis.com.au
® = Registered Trademark

9. DATE OF FIRST APPROVAL

17 January 2008

10. DATE OF REVISION

03 September 2019

Summary table of changes

Section	Summary of new information
4.4	Case reports of growth retardation
4.8	Reporting suspected adverse effects
4.9	Management of overdose
4.2	Monitoring Recommendations and Dose Adjustments addition *If the prior dose was 400 mg once daily, treatment should be discontinued.*