TASIGNA
NEW ZEALAND DATA SHEET

1 PRODUCT NAME

TASIGNA®150 mg and 200 mg Hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance(s)

150 mg hard capsules

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

200 mg hard capsules

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

Excipients with known effects

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

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules.

150 mg hard capsules

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

200 mg hard capsules

White to slightly yellowish powder in light yellow opaque hard gelatin capsules, size 0 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 (Ph+ CML) in chronic phase,
- treatment of chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in adult patients resistant to or intolerant to at least one 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.

Dose

Dosage in patients with newly diagnosed Ph+ CML-Chronic Phase (CP)

The recommended dose of TASIGNA is 300 mg twice daily (see section 5.2). Treatment should be continued as long as the patient continues to benefit.

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 and section 5.1).

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 molecular response 4.5 (MR4.5).

For patients who lose MR4.0 but not Major Molecular Response (MMR) 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 and Section 5.1).

Dosage in 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). Treatment should be continued as long as the patient continues to benefit.

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 and section 5.1).

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.

Patients with confirmed loss of MR 4.0 (two consecutive measures separated by at least 4 weeks showing loss of MR 4.0) or loss of 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 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 and section 5.1).

Monitoring recommendations and dose adjustments

A baseline electrocardiogram (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).

Increases in total serum cholesterol levels have been reported with Tasigna therapy (see section 4.4). 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). Blood glucose levels should be assessed prior to initiating Tasigna therapy and monitored during treatment.

Due to possible occurrence of Tumor 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).

TASIGNA may need to be temporarily withheld and/or dose reduced for haematological toxicities (neutropenia, thrombocytopenia) that are not related to underlying leukaemia (see 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 at 400 mg twice daily	ANC * <1 x 10^9/L and/or platelet counts <50 x 10^9/L	Stop TASIGNA, and monitor blood counts Resume within 2 weeks at prior dose if ANC >1 x 10^9/L and/or platelets >50 x 10^9/L 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	Stop TASIGNA, and monitor blood counts. Resume within 2 weeks at prior dose if ANC >1.0 x 10^9/L and/or platelets >20 x 10^9/L. 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-haematologic toxicity develops, 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 attempted.

Elevated serum lipase: For Grade 3 to 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 and Section 4.8).

Elevated bilirubin and hepatic transaminases: For Grade 3 to 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).

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

Special populations

Paediatric Patients (below 18 years)

The safety and efficacy in children and adolescents below the age of 18 years has not been established. See section 4.4.

Elderly patients (65 years of age or above)

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 of age.

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.

Patients with hepatic impairment

Hepatic impairment has a modest effect on the pharmacokinetics of nilotinib. Dose adjustment is not considered necessary in hepatically impaired subjects, but patients with hepatic impairment should be treated with caution (see Section 4.4).

Patients with cardiac disorders

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 (see Section 4.4).

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 Section 4.4, Section 4.5 and Section 5.2).

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 4.4 and Section 5.2).

TASIGNA may be given in combination with haematopoietic growth factors such as erythropoietin or granulocyte colony-stimulating factor (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 listed in Section 6.1.

4.4 Special warnings and precautions for use

Myelosuppression

Treatment with TASIGNA is often associated with thrombocytopenia, neutropenia and anaemia (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 Section 4.2).

QT Prolongation

In vitro data suggest that nilotinib has the potential to prolong cardiac ventricular repolarization (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 or 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 5 ms and 8 ms, respectively. QTcF of >500 ms was observed in 4 patients (<1% of these patients).

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 ms (CI ± 4 ms). No subject had a QTcF > 450 ms. 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 interval: therefore, concomitant administration should be avoided (see section 4.4).

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

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.

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 repolarization 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).

Fluid retention

Severe forms of drug-related fluid retention such as pleural effusion, pulmonary edema, 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 etiology should be evaluated and patients treated accordingly (see section 4.2).

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).

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 and section 5.1).

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 and section 5.1). 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). If a hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitor (a lipid lowering agent) is needed, please refer to the section 'Interaction with other medicinal products and other forms of interaction' before starting treatment since certain HMG CoA reductase inhibitors are also 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). If test results warrant therapy, physicians should follow their local standards of practice and treatment guidelines.

Drug 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). Should treatment with any of these agents be required, it is recommended that therapy with TASIGNA be interrupted if possible (see section 4.5). If transient interruption of treatment with TASIGNA is not possible, close monitoring of the individual for prolongation of the QT interval is indicated (see section 4.2, section 4.5, and section 5.2).

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 (see section 4.5).

Food Effect

The bioavailability of nilotinib is increased by food. TASIGNA must not be taken in conjunction with food (see section 4.2 and section 4.5) 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 and no food other than applesauce must be used (see section 4.2 and section 5.2).

Grapefruit juice and other foods that are known to inhibit CYP3A4 should be avoided at any time.

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. Clinical studies have excluded patients with alanine transaminase (ALT) and/ or aspartate aminotransferase (AST) > 2.5 (or > 5, if related to disease) times the upper limit of the normal range and/ or total bilirubin >1.5 times the upper limit of the normal range. Metabolism of nilotinib is mainly hepatic. Caution is recommended in patients with hepatic impairment (see monitoring recommendations in section 4.2).

Use in Paediatrics

There have been case reports of growth retardation in paediatric patients treated with TASIGNA.

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).

Total gastrectomy

The bioavailability of nilotinib might be reduced in patients with total gastrectomy (see section 5.2). More frequent follow-up of these patients should be considered.

Tumor lysis syndrome

Cases of tumor lysis syndrome (TSL) have been reported in patients treated with TASIGNA. For monitoring recommendations please refer to Dosage and method of administration section.

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.

4.5 Interaction with other medicinal products and other forms of interaction

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

Drugs that may increase nilotinib serum concentrations

In a Phase I study of nilotinib given in combination with imatinib (a substrate of P-gp and CYP3A4), both drugs had a slight inhibitory effect on CYP3A4 and/or Pgp. 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) (see section 4.2 and section 4.4 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 nilotinib 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, 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 Cmax 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 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 an 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, an 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

Nilotinib is identified as a competitive inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2D6 and UGT1A1 *in vitro*, with Ki value being lowest for CYP2C9 (Ki=0.13 microM). Enzyme induction studies indicate that nilotinib can be considered to be an *in vitro* inducer of CYP2B6, CYP2C8 and CYP2C9 activities.

In CML patients, nilotinib administered at 400 mg twice daily for 12 days increased the systemic exposure of oral 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) 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, sirolimus and tacrolimus) when co-administered with nilotinib.

In 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.

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).

Other interactions that may affect serum concentrations

The 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.

The absorption and the bioavailability of nilotinib are increased if it is taken with food, resulting in higher serum concentration (see section 4.2, section 4.4, and section 5.3).

Grapefruit juice and other foods that are known to inhibit CYP3A4 should be avoided at any time.

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk Summary

TASIGNA can cause fetal harm when administered to a pregnant woman. There are no adequate data on the use of TASIGNA in pregnant women. Reproductive studies in rats and rabbits have demonstrated that nilotinib induced embryo-toxicity and/or feto-toxicity (following prenatal exposure to nilotinib) at exposures equal to the one achieved in humans at the maximum recommended human dose of 400 mg twice daily. TASIGNA should not be used during pregnancy unless necessary. 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 section 4.2 and section 4.4).

Animal Data

Nilotinib did not induce teratogenicity, but did show embryo- and foetotoxicity at doses which also showed maternal toxicity. Increased postimplantation loss was observed in both the fertility study, with treatment of both males and females, and in the embryotoxicity study with the treatment of females. Embryo-lethality and foetal effects (mainly decreased foetal weights, visceral and skeletal variations) in rats and increased resorption of foetuses 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.

Contraception

Females of reproductive potential must be advised to use an 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.

Lactation

Risk Summary

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

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.

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 Adverse effects with a potential impact on the ability to safely drive or use machines should refrain from these activities as long as these Adverse effects persist (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The nilotinib 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 listed indications (see Table 2 and 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 randomized phase III study in patients with newly diagnosed Ph+ CML in chronic phase treated at the recommended dose of 300 mg twice daily (n=279). The median time on treatment was 60.5 months (range 0.1 – 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 ms. 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 ms 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 ms 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 left ventricular ejection fraction (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%), hyperbilirubinemia (16%), aspartate aminotransferase increased (12%), lipase increased (11%), blood bilirubin increased (10%), hyperglycemia (4%), hypercholesterolemia (3%), and hypertriglyceridemia (<1%). See Table 3 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 multicenter 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 3 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.

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-month analysis						24-month 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

			Newly Diagnosed Ph+ CML-CP						Resistant or Intolerant Ph+ CML-CP and CML-AP			
			60-month analysis						24-month 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 %**
	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 a frequency of less than 5% (common is ≥1/100 and <1/10; uncommon is ≥1/1,000 to <1/100; single events are captured as frequency not known). For laboratory abnormalities, very common events (≥1/10) not included in Table 2 are also reported. These adverse reactions are included based on clinical relevance and ranked in decreasing order of 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:	
Unknown frequency:	hypersensitivity.
Endocrine Disorders:	
Uncommon:	hyperthyroidism, hypothyroidism.
Frequency not known:	hyperparathyroidism secondary, thyroiditis.
Metabolism and Nutrition Disorders:	
Very common:	hypophosphatemia (including blood phosphorus decreased).
Common:	electrolyte imbalance (including hypomagnesaemia, hyperkalaemia, hypokalaemia, hyponatraemia, hypocalcaemia, hypercalcaemia, hyperphosphataemia), diabetes mellitus, hyperglycaemia hypercholesterolaemia, hyperlipidaemia, hypertriglyceridemia.
Uncommon:	gout, dehydration, increased appetite, dyslipidemia.
Frequency not known:	hyperuricemia, hypoglycemia.

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 hemorrhage.
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, 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 erythrodysaesthesia 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 increased, aspartate aminotransferase 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 creatine 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.

Laboratories abnormalities

Clinically relevant or severe abnormalities of routine haematologic or biochemistry laboratory values are presented in Table 4.

Table 4 Grade 3/4 Laboratory Abnormalities

	Newly diagnosed Ph+ CML-CP			Resistant or intolerant Ph+	
	TASIGNA 300 mg twice daily N = 279	**TASIGNA 400 mg twice daily N = 277**	**IMATINIB 400 mg once daily N = 280**	**CML-CP N=321**	**CML-AP N=137**
Haematologic 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	8%	10%	4%	18%	18%
– Elevated SGOT (AST)	1%	3%	1%	3%	2%
– Elevated SGPT (ALT)	4%	9%	3%	4%	4%
– Hypophosphataemia	8%	10%	10%	17%	15%

	Newly diagnosed Ph+ CML-CP			Resistant or intolerant Ph+	
	TASIGNA 300 mg twice daily N = 279	**TASIGNA 400 mg twice daily N = 277**	**IMATINIB 400 mg once daily N = 280**	**CML-CP N=321**	**CML-AP N=137**
– 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

Musculoskeletal symptoms

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: Tumor lysis syndrome, facial paralysis.

Reporting of suspected adverse reactions

The reporting suspected adverse reactions after the authorisation of the medicine is important. It allows for continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to Medsafe via the following web site: https//nzphvc.otago.ac.nz/ reporting/.

4.9 Overdose

Symtoms

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 advice on the management of overdose, please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents - Protein-tyrosine kinase inhibitor

ATC code: L01XE08.

Mechanism of action

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 leukaemia 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. As a consequence of this biochemical activity, nilotinib selectively inhibits the proliferation and induces apoptosis in cell lines and in primary Philadelphia-chromosome positive leukaemia cells from CML patients. In murine models of CML, as a single agent nilotinib reduces tumour burden and prolongs survival following oral administration.

Pharmacodynamics (PD)

TASIGNA has little or no effect against the majority of other protein kinases examined, including Src, except for the platelet-derived growth factor (PDGF), KIT, colony stimulating factor 1 receptor (CSF-1R), discoidin domain receptor (DDR) 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 5).

Table 5 Kinase Profile of Nilotinib (Phosphorylation IC_{50} nM)

BCR-ABL	PDGFR	KIT
20	69	210

Clinical studies

Newly diagnosed Ph+ CML-CP

An open label, multicenter, randomized 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. 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. In each treatment arm, more than 80% of patients had received treatment for longer than 12 months. 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 real-time quantitative polymerase chain reaction (RQ-PCR), which corresponds to a ≥ 3 log reduction of BCR-ABL transcript from standardized baseline.

The primary efficacy endpoint, Major Molecular Response (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). 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 (42.7% vs. 22.3%, p<0.0001), Table 5.

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 6.

Table 6 MMR 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 (%)**
MMR at 12 months	125 (44.3)[1]	120 (42.7)[1]	63 (22.3)
95% CI for response	[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

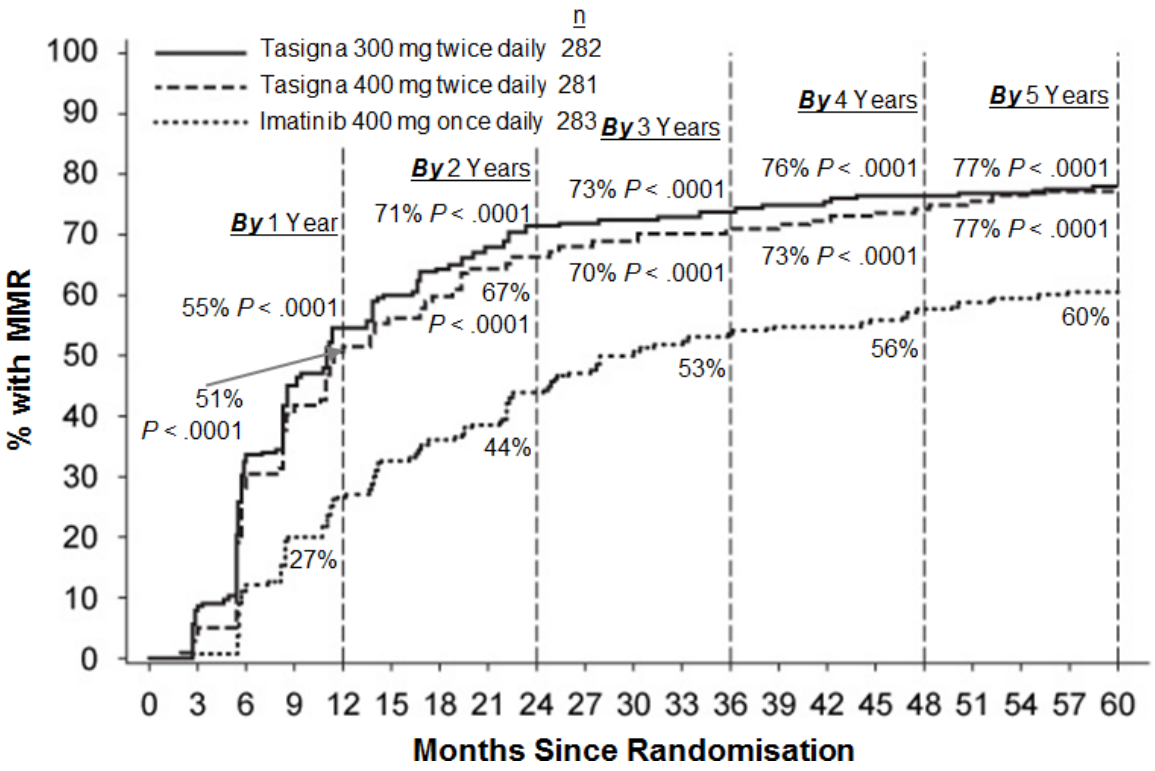
[2] Only patients who were in MMR at a specific time point are included as responders for that time point. A total of 199 (35.2%) of all patients were not evaluable for MMR at 36 months (87 in the nilotinib 300 mg BID group and 112 in the imatinib group) due to missing/unevaluable PCR assessments (n=17),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

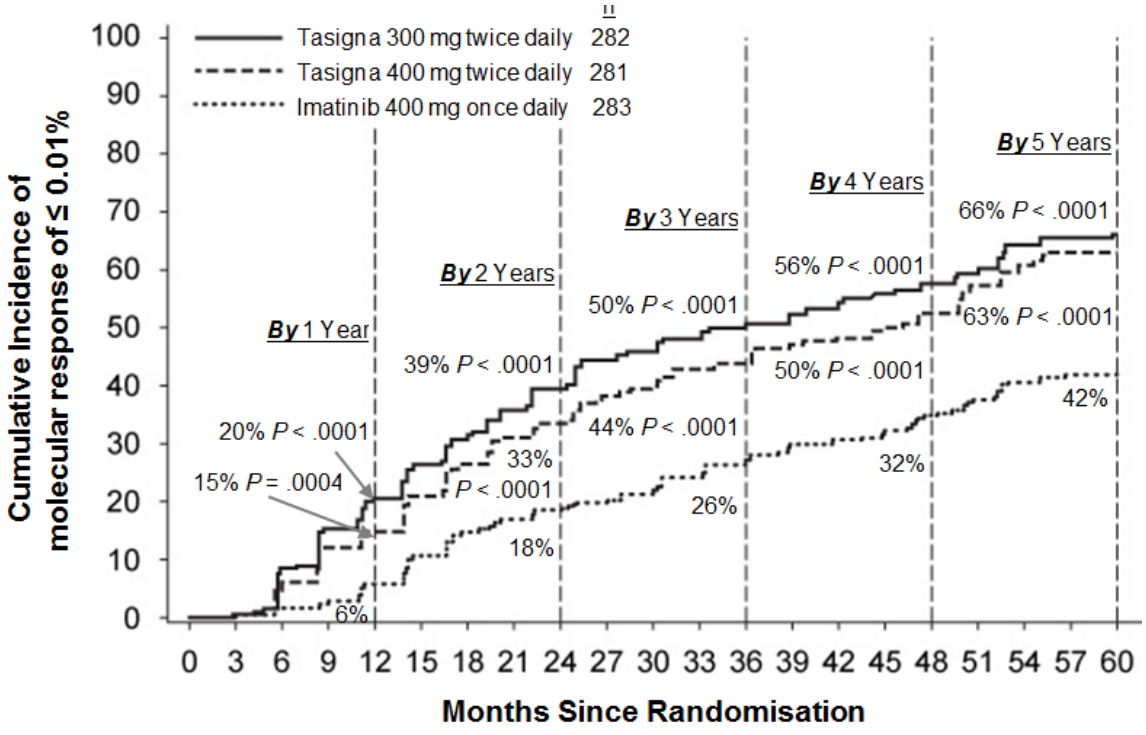
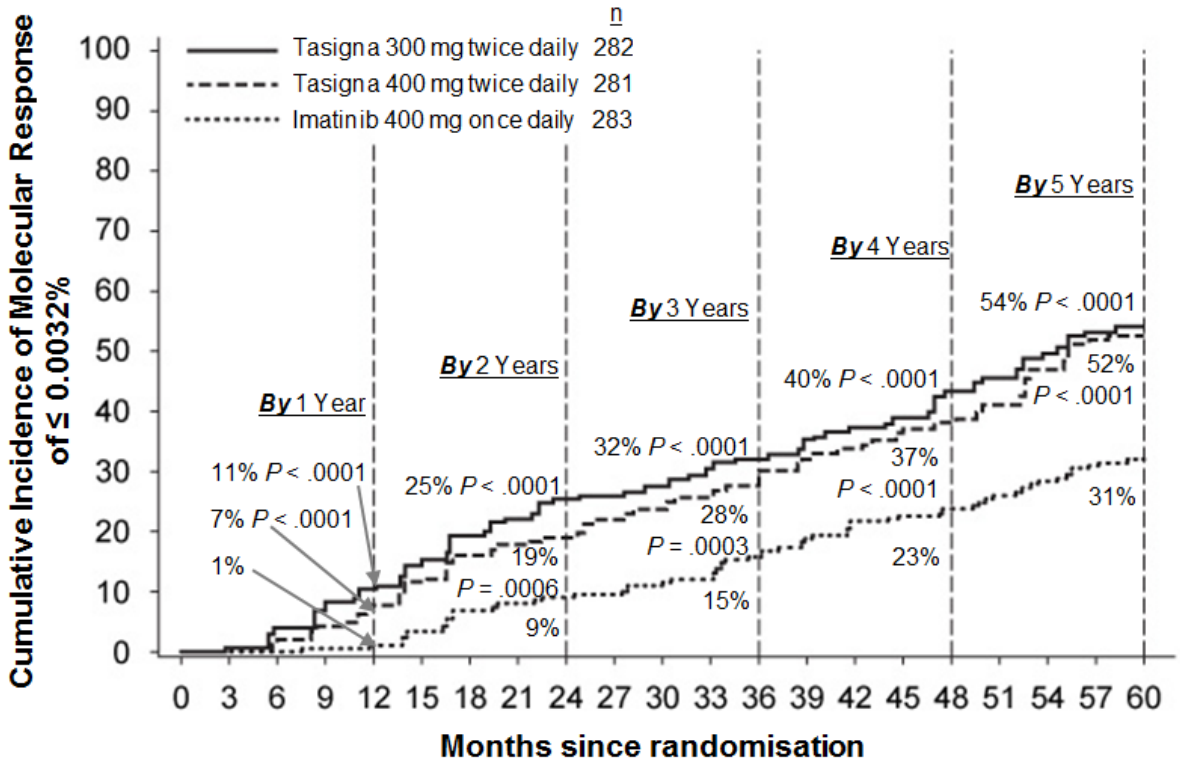


Figure 3 Cumulative incidence of molecular response of ≤ 0.0032% (4.5 log reduction)



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 8.

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 8 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 95% CI for response	226 (80.1) [75.0,84.6]	219 (77.9) [72.6,82.6]	184 (65.0) [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 95% CI for response	245 (86.9%) [82.4, 90.6]	238 (84.7%) [79.9, 88.7]	218 (77.0%) [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 twice daily (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 multicenter 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 CP patients and 137 AP patients enrolled. Median duration of treatment was 561 days and 264 days, respectively (see Table 9). 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. Dose escalation to 600 mg twice daily was allowed.

Table 9 Duration of Exposure with TASIGNA

	Chronic Phase N = 321	**Accelerated Phase N = 137**
Median duration of therapy in days (25^{th} – 75^{th} percentiles)	561 (196-852)	264 (115-595)

Resistance to imatinib included failure to achieve a complete haematologic response (CHR) (by 3 months), cytogenetic response (by 6 months) or major cytogenetic response (by 12 months) or progression of disease after a previous cytogenetic or haematologic response. Imatinib intolerance included patients who discontinued imatinib because of toxicity and were not in major cytogenetic response at time of study entry.

Overall, 73% of patients were imatinib-resistant while 27% were imatinib-intolerant. The majority of patients had a long history of CML that included extensive prior treatment with other antineoplastic agents such as imatinib, hydroxyurea, interferon, and some that had even failed stem cell transplant (Table 10). The median highest prior imatinib dose had been 600 mg/day for 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 10 CML Disease History Characteristics

	Chronic Phase (n = 321)	Accelerated Phase (n = 137)*
Median time since diagnosis in months (range)	68 (5-275)	70 (2-298)
Imatinib		
Resistant	226 (70%)	109 (80%)
Intolerant without MCyR	95 (30%)	27 (20%)
Median time of imatinib treatment in days (25^{th} – 75^{th} percentiles)	975 (519-1,488)	857 (424-1,497)
Prior Hydroxyurea	83%	91%
Prior Interferon	58%	50%
Prior organ transplant	7%	8%

* One patient had missing information for imatinib-resistant/tolerant status

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. CHR in CP patients was evaluated as a secondary endpoint. The primary endpoint in the AP patients was overall confirmed haematologic response (HR), defined as either a complete haematologic response, no evidence of leukaemia or return to chronic phase.

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 were sustained The median time to achieve MCyR 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%-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 and median duration of CHR has not been reached.

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 55%. Most responders achieved a HR early with TASIGNA treatment (median 1.0 months) and these have been durable (median duration of confirmed HR was 21.5 months). Of the patients who achieved HR, 49% (95% CI: 35% to 62%) were maintaining response at 24 months. MCyR rate was 32% with a median time to response of 2.8 months. Of the patients who achieved MCyR, 66% (95% CI: 50%-82%) were maintaining response at 24 months. Median duration of MCyR has not been reached. The rates of response for the two treatment arms are reported in Table 11.

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

Table 11 Response 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)
Haematologic Response (%)						
Overall (95%CI)	-	-	-	56 (35-75)	55 (45-65)	55 (47-64)
Complete	90 (79-97)	72 (64-79)	76[1] (70-82)	37	30	31
NEL	-	-	-	15	11	12
Return to CP	-		-	4	14	12
Cytogenetic Response (%)						
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

NEL = no evidence of leukaemia/marrow response
[1] 114 CP patients had a CHR at baseline and were therefore not assessable for complete haematologic response
* One patient had missing information for imatinib-resistant/tolerant status

Separate treatment arms were also included in the Phase II study 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 not intolerant. In 22 CP patients evaluated for efficacy TASIGNA induced a 32% MCyR rate and a 50% CHR rate. In 11 AP patients evaluated for efficacy, treatment induced a 36% overall HR rate.

After imatinib failure, 24 different BCR-ABL mutations 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.

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.

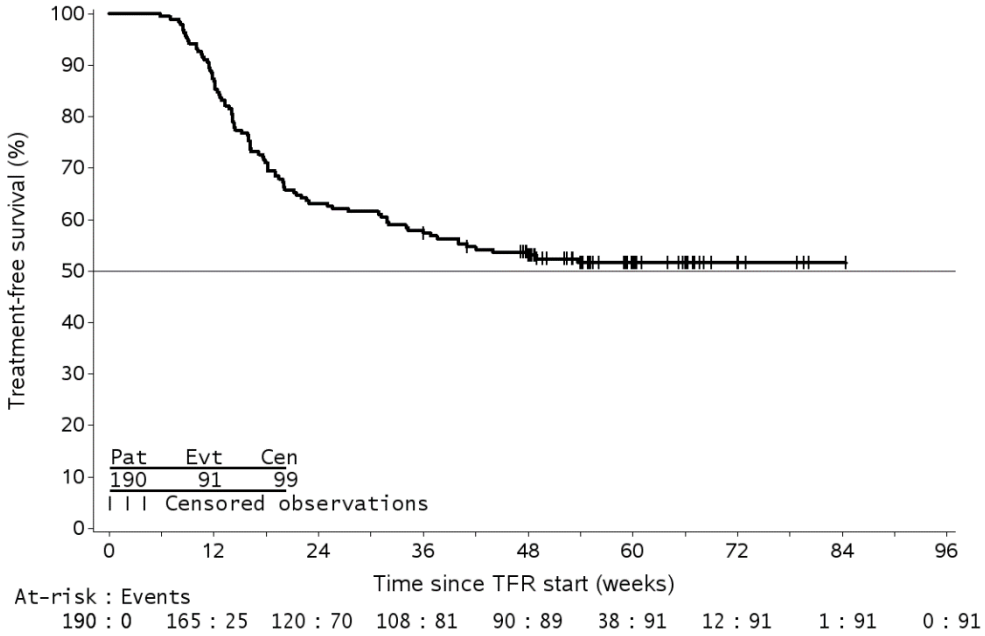
Of the 86 patients who restarted treatment due to loss of MMR in the TFR phase, 85 patients (98.8%) regained MMR, (one patient discontinued study permanently due to subject decision) and 76 patients (88.4%) regained MR4.5 by the time of the cut-off date.

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 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.

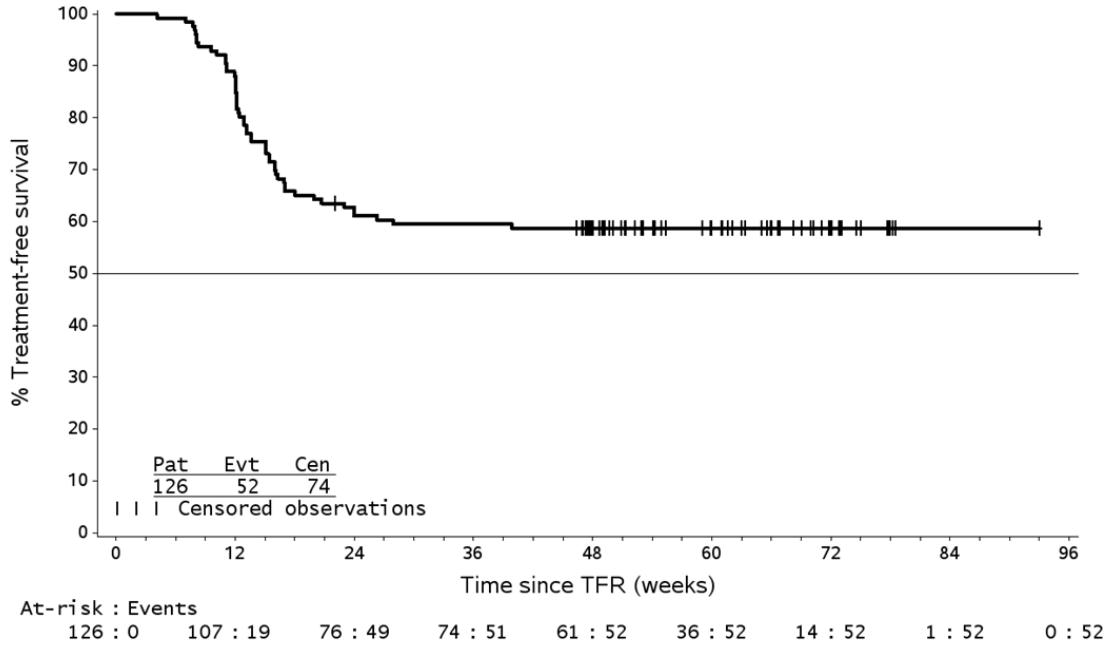
Among the 53 patients who discontinued from the TFR phase due to confirmed loss of MR4.0 or loss of MMR, 51 patients restarted Tasigna therapy and 2 patients permanently discontinued from the study. Of the 51 patients who restarted Tasigna treatment due to confirmed loss of MR4.0 or loss of MMR in the 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.

Food effect

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, section 4.4, and section 4.5). 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 apple sauce, was shown to be bioequivalent with a single dose administration of 2 intact capsules of 200 mg.

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 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.

Distribution

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

Biotransformation

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.

Elimination

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

Characteristics in patients

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 PK with daily dosing was approximately 17 hours. Inter-patient variability in nilotinib PK was moderate to high.

5.3 Preclinical safety data

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

Safety pharmacology and repeated dose toxicity

Nilotinib did not have effects on central nervous system (CNS) or respiratory functions. *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.

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. Mainly reversible increases in cholesterol levels were seen in rats, dogs and monkeys.

Carcinogenicity and mutagenicity

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.

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 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 (NOEL) 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).

Juvenile animal studies

In a juvenile development study, nilotinib was administered via oral gavage to juvenile rats from the first week postpartum through young adult (day 70 postpartum) at doses of 2, 6 and 20 mg/kg/day. Effects were limited to the dose of 20 mg/kg/day and consisted of reductions in body weight parameters and food consumption with recovery after dosing ceased. The NOEL in juvenile rats was considered to be 6 mg/kg/day. Overall, the toxicity profile in juvenile rats was comparable to that observed in adult rats.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

150 mg hard capsules

Capsule content: lactose monohydrate; crospovidone; poloxamer 188; silica colloidal, anhydrous/colloidal silicon dioxide; magnesium stearate

Capsule shell: gelatin; titanium dioxide (E 171); iron oxide, red (E 172), iron oxide, yellow (E 172)

Printing ink: shellac; iron oxide, black (E 172); n-butyl alcohol; propylene glycol; dehydrated ethanol; isopropyl alcohol; ammonium hydroxide.

200 mg hard capsules

Capsule content: lactose monohydrate; crospovidone; poloxamer 188; silica colloidal, anhydrous/colloidal silicon dioxide; magnesium stearate

Capsule shell: gelatin; titanium dioxide (E 171); iron oxide, yellow (E 172)

Printing ink: shellac; dehydrated alcohol; isopropyl alcohol; butyl alcohol; propylene glycol; strong ammonia solution; potassium hydroxide; purified water; iron oxide, red (E 172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

150 mg hard capsules

36 months

200 mg hard capsules

36 months

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package.

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

6.5 Nature and contents of container

- 150 mg hard capsules: PVC/PVDC blisters
- 200 mg hard capsules: PVC/PVDC and PA/AL/PVC blisters

6.6 Special precautions for disposal and other handling

No special requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Novartis New Zealand Limited

PO Box 99102

Newmarket, Auckland 1149

Telephone: 0800 354 335

Fax number: (09) 361 8181

E-mail: medinfo.phauno@novartis.com

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to first distribute the medicine: 23 August 2010

10. DATE OF REVISION OF THE TEXT

6 April 2022

Summary table of changes

Section changes	Summary of new information
6.1	List of excipients