NOVARTIS

Regulatory Affairs

TASIGNA® (nilotinib)
50 mg, 150 mg and 200 mg Hard capsules

PRESCRIBING INFORMATION

Version 2.2

NOTICE

The Novartis Core Data Sheet (CDS) displays the company's current position on important characteristics of the product, including the Core Safety Information according to ICH E2C.

The Novartis CDS contains all relevant information relating to indications, dosage, pharmacology and Core Safety Information which Novartis requires to be listed for the product in all countries where the product is registered.

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1 Tradename

TASIGNA® 50 mg hard capsules

TASIGNA® 150 mg hard capsules

TASIGNA® 200 mg hard capsules

2 Description and composition

Pharmaceutical form

Hard capsules

50 mg hard capsules

White to yellowish powder in hard gelatin capsule with red opaque cap and light yellow opaque body, size 4 with black radial imprint “NVR/ABL” on cap.

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

Active substances

50 mg hard capsules: Each capsule contains 50 mg nilotinib base (as hydrochloride monohydrate) [119].

150 mg hard capsules: Each capsule contains 150 mg nilotinib base (as hydrochloride, monohydrate) [73].

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

Excipients

50 mg hard capsules [119]

Capsule content: Lactose monohydrate; Crospovidone; Poloxamer; Silica, colloidal anhydrous; Magnesium stearate.

Capsule shell: Gelatin; Titanium dioxide (E171); Iron oxide, red (E172); Iron oxide, yellow (E172).

Printing ink: Shellac; Iron oxide, black (E172); Propylene glycol; Ammonium hydroxide.

150 mg hard capsules [73]

Capsule content: Lactose monohydrate; Crospovidone; Poloxamer; 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; 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; Titanium dioxide; Industrial methylated spirit; Iron oxide, red (E 172), Iron oxide, black (E172).

Information might differ in some countries.

3 Indications

TASIGNA hard capsules are indicated for the:

- treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase [74]. Patients who have been treated with TASIGNA for at least 3 years and have achieved a sustained deep molecular response may be eligible for treatment discontinuation (see sections 4 Dosage regimen and administration and 12 Clinical studies) [115].
- treatment of chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukemia (Ph+ CML) in adult patients resistant to or intolerant to at least one prior therapy including imatinib [1]. Ph+ CML patients in chronic phase, who have been previously treated with imatinib and whose treatment has been switched to TASIGNA for at least 3 years and have achieved a sustained deep molecular response may be eligible for treatment discontinuation (see sections 4 Dosage regimen and administration and 12 Clinical studies) [115].
- treatment of pediatric patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase [120].
- treatment of pediatric patients with chronic phase Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) with resistance or intolerance to prior therapy including imatinib [120].

4 Dosage regimen and administration

TASIGNA is available in three dosage strengths (50 mg, 150 mg and 200 mg).

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

TASIGNA may be given in combination with hematopoietic 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 [3].

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 [111].

General target population

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

The recommended dose of TASIGNA is 300 mg twice daily (see section 12 Clinical studies). Treatment should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs [74].

Dosage in newly diagnosed Ph+ CML-CP adult patients who have achieved a sustained deep molecular response (MR4.5) [115,116]

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 sections 6 Warnings and precautions and 12 Clinical studies).

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 sections 6 Warnings and precautions and 12 Clinical studies).

Dosage in adult 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 12 Clinical studies). Treatment should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs [2].

Dosage in Ph+ CML-CP adult patients who have achieved a sustained deep molecular response (MR4.5) on TASIGNA following prior imatinib therapy [115,117]

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 sections 6 Warnings and precautions and 12 Clinical studies).

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 MR4.0 (two consecutive measures separated by at least 4 weeks showing loss of MR4.0) 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 MR4.0 is re-established (see sections 6 Warnings and precautions and 12 Clinical studies).

Dosage in pediatric patients with newly diagnosed Ph+ CML-CP or resistant or intolerant Ph+ CML-CP

Dosing in pediatric patients is individualized and is based on body surface area (mg/m^2). The recommended dose of TASIGNA is 230 mg/m^2 twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg) (see Table 4-1). Different strengths of TASIGNA capsules can be combined to attain the desired dose. Treatment should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs [120].

There is no experience with treatment of pediatric patients below 2 years of age.

Table 4-1 Pediatric dosing scheme of TASIGNA 230 mg/m² twice daily

Body Surface Area (BSA)	Dose in mg (twice daily)
Up to 0.32 m^2	50 mg
0.33 to 0.54 m^2	100 mg
0.55 to 0.76 m^2	150 mg
0.77 to 0.97 m^2	200 mg
0.98 to 1.19 m^2	250 mg
1.20 to 1.41 m^2	300 mg
1.42 to 1.63 m^2	350 mg
≥1.64 m^2	400 mg

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. Hypokalemia or hypomagnesemia must be corrected prior to TASIGNA administration and potassium and magnesium blood levels should be monitored periodically during therapy, particularly in patients at risk for these electrolyte abnormalities (see section 6 Warnings and precautions) [57].

Increases in total serum cholesterol levels have been reported with TASIGNA therapy (see section 6 Warnings and precautions). 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 [79,110].

Increases in blood glucose levels have been reported with TASIGNA therapy (see section 6 Warnings and precautions). Blood glucose levels should be assessed prior to initiating TASIGNA therapy and monitored during treatment [99].

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 7 Adverse drug reactions) [81].

TASIGNA may need to be temporarily withheld and/or dose reduced for hematological toxicities (neutropenia, thrombocytopenia) that are not related to underlying leukemia (see Table 4-2) [3,58].

Table 4-2 Dose adjustments for neutropenia and thrombocytopenia [75]

Adult patients with: - 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 × 10^9/L and/or platelet counts <50 × 10^9/L	1. Stop TASIGNA, and monitor blood counts. 2. Resume within 2 weeks at prior dose if ANC >1 × 10^9/L and/or platelets >50 × 10^9/L. 3. If blood counts remain low, a dose reduction to 400 mg once daily may be required.
Adult patients with resistant or intolerant CML in	ANC* <0.5 × 10^9/L and/or	1. Stop TASIGNA, and monitor blood counts.

accelerated phase at 400 mg twice daily	platelet counts <10 × 10^9/L	2. Resume within 2 weeks at prior dose if ANC >1.0 × 10^9/L and/or platelets >20 × 10^9/L. 3. If blood counts remain low, a dose reduction to 400 mg once daily may be required.
Pediatric patients with: - Newly diagnosed CML in chronic phase at 230 mg/m^2 twice daily - Resistant or intolerant CML in chronic phase at 230 mg/m^2 twice daily	ANC* <1 × 10^9/L and/or platelet counts <50 × 10^9/L	1. Stop TASIGNA and monitor blood counts. 2. Resume within 2 weeks at prior dose if ANC >1.5 × 10^9/L and/or platelets >75 × 10^9/L. 3. If blood counts remain low, a dose reduction to 230 mg/m^2 once daily may be required. 4. If event occurs after dose reduction, consider discontinuing treatment.

**ANC = absolute neutrophil count*

If clinically significant moderate or severe non-hematologic toxicity develops, dosing should be interrupted, and patients should be monitored and treated accordingly. If the prior dose was 300 mg twice daily in adult newly diagnosed patients with CML-CP or 400 mg twice daily in adult patients with resistant or intolerant CML-CP and CML-AP or 230 mg/m^2 twice daily in pediatric patients, dosing may be resumed at 400 mg once daily in adult patients or at 230 mg/m^2 once daily in pediatric patients once the toxicity has resolved. If the prior dose was 400 mg once daily in adult patients or 230 mg/m^2 once daily in pediatric patients, treatment should be discontinued. If clinically appropriate, re-escalation of the dose in adult patients to 300 mg (newly diagnosed Ph+ CML-CP) or 400 mg (resistant or intolerant Ph+ CML-CP and CML-AP) twice daily or to 230 mg/m^2 twice daily in pediatric patients should be attempted.

Elevated serum lipase: For Grade 3 to 4 lipase elevations, doses in adult patients should be reduced to 400 mg once daily or interrupted. In pediatric patients, treatment must be interrupted until the event returns to Grade ≤1. Thereafter, if the prior dose was 230 mg/m^2 twice daily, treatment can be resumed at 230 mg/m^2 once daily. If the prior dose was 230 mg/m^2 once daily, treatment should be discontinued. Serum lipase levels should be tested monthly or as clinically indicated (see sections 6 Warnings and precautions and 7 Adverse drug reactions).

***Elevated bilirubin and hepatic transaminases*:** For Grade 3 to 4 bilirubin or hepatic transaminase elevations in adult patients, doses should be reduced to 400 mg once daily or interrupted [74]. For Grade ≥2 bilirubin elevations or Grade ≥3 hepatic transaminase elevations in pediatric patients, treatment must be interrupted until the levels return to Grade ≤1. Thereafter, if the prior dose was 230 mg/m^2 twice daily, treatment can be resumed at 230 mg/m^2 once daily. If the prior dose was 230 mg/m^2 once daily, and recovery to Grade ≤1 takes longer than 28 days, treatment should be discontinued. Bilirubin and hepatic transaminases levels should be tested monthly or as clinically indicated (see section 7 Adverse drug reactions) [2].

Special populations

Renal impairment

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

Since nilotinib and its metabolites are not renally excreted, a decrease in total body clearance is not anticipated in patients with renal impairment [4].

Hepatic impairment

Hepatic impairment has a modest effect on the pharmacokinetics of nilotinib. Dose adjustment is not considered necessary in hepatically impaired patients. Patients with hepatic impairment should be treated with caution (see section 6 Warnings and precautions) [59,61].

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 6 Warnings and precautions).

Pediatric patients (below 18 years)

The safety and efficacy of TASIGNA in pediatric patients with Ph+ CML-CP from 2 to less than 18 years of age have been established (see sections 7 Adverse drug reactions, 11 Clinical pharmacology, and 12 Clinical studies). There is no experience in pediatric patients below 2 years of age or in pediatric patients with Ph+ CML-AP or blast crisis (BC) [120].

Geriatric 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 [76]. 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.

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 two 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 6 Warnings and precautions and section 8 Interactions) [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 11 Clinical pharmacology) [68].

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

5 Contraindications

TASIGNA is contraindicated in patients with known hypersensitivity to nilotinib or to any of the excipients.

6 Warnings and precautions

Myelosuppression

Treatment with TASIGNA is often associated with thrombocytopenia, neutropenia and anemia (NCI CTC Grade 3/4). The occurrence is more frequent in patients with imatinib-resistant or intolerant CML and in particular in patients with CML-AP. Complete blood counts should be performed every two weeks for the first 2 months and then monthly thereafter, or as clinically indicated. Myelosuppression was generally reversible and usually managed by withholding TASIGNA temporarily or reducing the dose (see section 4 Dosage regimen and administration) [2,77].

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 msec and no events of Torsades de Pointes were observed [77].

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 msec and 8 msec, respectively. QTcF of >500 msec was observed in 4 patients (<1% of these patients) [5,69].

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 msec. In addition, no clinically relevant arrhythmias were observed during the conduct of the trial. In particular, no episodes of Torsades de Pointes (either transient or sustained) were observed [6].

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 6 Warnings and precautions: Food effects and section 8 Interactions).

The presence of hypokalemia and hypomagnesemia may place patients at risk of developing QT prolongation (see section 4 Dosage regimen and administration) [57].

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 [57].

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 [57]. Based on post-marketing exposure in patient-years, the estimated reporting rate for spontaneous reports of sudden death is 0.02% per patient-year [69]. No cases of sudden deaths have been reported in the newly diagnosed Ph+ CML-CP Phase III study [77].

Cardiovascular events

Cardiovascular events were reported in a 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 Dosage regimen and administration) [103,107].

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 [105]. 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 Dosage regimen and 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 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 7 Adverse drug reactions) [114].

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 [114].

Special monitoring of Ph+ CML-CP adult patients who have achieved a sustained deep molecular response [115]

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 MR4.5. BCR-ABL transcript levels must be assessed prior to and during treatment discontinuation (see sections 4 Dosage regimen and administration and 12 Clinical studies).

Loss of MMR or confirmed loss of MR4.0 (two consecutive measures separated by at least 4 weeks showing loss of MR4.0) will trigger treatment re-initiation within 4 weeks of when loss of remission is known to have occurred. Frequent monitoring of BCR-ABL transcript levels and complete blood count with differential is required to detect possible loss of remission (see sections 4 Dosage regimen and administration and 12 Clinical studies). For patients who fail to achieve MMR after three months of treatment re-initiation, BCR-ABL kinase domain mutation testing should be performed.

Special populations

Pediatric patients (below 18 years)

The long-term effects of prolonged treatment with TASIGNA in pediatric patients are unknown [120]. There have been case reports of growth retardation in pediatric patients treated with TASIGNA. Close monitoring of growth in pediatric patients under TASIGNA treatment is recommended [125].

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 (see section 7 Adverse drug reactions). 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 Dosage regimen and administration) [110]. If a hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitor (a lipid lowering agent) is needed, refer to section 8 Interactions, before starting treatment since certain HMG-CoA reductase inhibitors are metabolized by the CYP3A4 pathway [104].

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 Dosage regimen and administration). If test results warrant therapy, physicians should follow their local standards of practice and treatment guidelines [99,107].

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 sections 4 Dosage regimen and administration and 8 Interactions). Should treatment with any of these agents be required, it is recommended that therapy with TASIGNA be interrupted if possible (see section 8 Interactions). If transient interruption of treatment with TASIGNA is not possible, close monitoring of the individual for prolongation of the QT interval is indicated (see sections 4 Dosage regimen and administration, 8 Interactions and 11 Clinical pharmacology) [3].

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 8 Interactions).

Food effects

The bioavailability of nilotinib is increased by food. TASIGNA must not be taken in conjunction with food (see sections 4 Dosage regimen and administration and 8 Interactions) and should be taken 2 hours after a meal. No food should be consumed for at least one hour after the dose is taken [68].

Grapefruit juice and other foods that are known to inhibit CYP3A4 should be avoided at any time [3].

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 [59]. 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 Dosage regimen and administration) [61].

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 Dosage regimen and administration) [75].

Total gastrectomy

The bioavailability of nilotinib might be reduced in patients with total gastrectomy (see section 11 Clinical pharmacology). More frequent follow-up of these patients should be considered [66].

Tumor lysis syndrome

Cases of TLS have been reported in patients treated with TASIGNA [81]. For monitoring recommendations refer to section 4 Dosage regimen and administration.

7 Adverse drug reactions

Summary of the safety profile

The nilotinib safety profile described below is based on data from adult patients with newly diagnosed Ph+ CML-CP in a randomized, open label, active comparator-controlled Phase III trial and adult patients with resistant or intolerant Ph+ CML-CP and CML-AP which served as a basis for the listed indications (see Table 7-1 and section 3 Indications). Safety information from two TASIGNA treatment discontinuation studies in adult patients [116,117] and from a Phase III study in adult patients with Ph+ CML in chronic phase with suboptimal response to imatinib [118] is also provided.

In adult patients with newly diagnosed Ph+ CML-CP

The data reported below reflect exposure to TASIGNA from a randomized Phase III study in adult 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 to 70.8 months) [75,79,85,88,94,107].

Non-hematologic 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) [107]. 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 [75,79,88,94,107]. 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 [77,79,85,88,94,107].

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 Torsades de Pointes were observed. QTcF increase from baseline that exceeds 60 msec was observed in 5 patients while on TASIGNA (one in the 300 mg twice daily treatment group and four in the 400 mg twice daily treatment group) [77,85,88,94].

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 [77,79,96,107].

No sudden deaths have been reported in any treatment group [77,85,88,94,107].

In the nilotinib 300 mg twice daily group, haematologic ADRs include myelosuppression: thrombocytopenia (18%), neutropenia (15%), and anaemia (8%) [77,79,88,94,107]. 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%) [110]. See Table 7-3 for Grade 3/4 laboratory abnormalities.

Discontinuation due to adverse drug reactions was observed in 10% of patients [77,79,85,88,94,107].

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

The data reported below reflect exposure to TASIGNA in 458 adult 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 [5,51,70,71].

Non-haematologic 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 [51,69]. 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 [51]. Gastrointestinal and central nervous system (CNS) haemorrhage was reported in 1% and <1% of patients, respectively [5].

QTcF exceeding 500 msec was observed in this study in 4 patients (<1%). No episodes of Torsades de Pointes (transient or sustained) were observed [5,69].

Haematologic ADRs include myelosuppression: thrombocytopenia (31%), neutropenia (17%), and anaemia (14%). See Table 7-3 for Grade 3/4 laboratory abnormalities.

Discontinuation due to adverse drug reactions was observed in 16% of CP and 10% of AP patients [5,51,69].

In adult patients with Ph+ CML-CP who have not achieved a molecular response greater than or equal to a 4.5-log reduction with imatinib treatment [118]

The data reported below were generated in a randomized, open-label, Phase III study where adult male and female patients diagnosed with Ph+ CML-CP and after two years of imatinib therapy were exposed to TASIGNA 400 mg twice daily versus imatinib 400 mg or 600 mg once daily for 48 months. Patients randomized to the imatinib arm received the same dose of imatinib as prior to randomization. The median duration of exposure was 47.2 months in the TASIGNA arm and 37.0 months and 26.7 months in the 400 mg and 600 mg dose cohorts of the imatinib arm, respectively.

The adverse drug reactions reported by at least 20% of the patients in the TASIGNA group and more frequently compared to the imatinib group were headache, rash, and pruritus. A greater proportion of patients in the TASIGNA group reported adverse events (AEs) leading to discontinuation and AEs requiring dose adjustment/interruption compared to those in the imatinib group. Increases in bilirubin and transaminases were commonly reported following TASIGNA treatment.

Up to the 48-month cut-off date, three on-treatment deaths have been observed (two in the TASIGNA arm and one in the imatinib arm). Three patients died more than 28 days after study drug discontinuation (one in the TASIGNA arm and two in the imatinib arm).

QTc intervals >450 ms were observed in 4 patients receiving TASIGNA therapy on Day 8. No patient had a QTc interval >480 ms. Increases in QTc interval from baseline of >30 ms were reported for 8 patients (7.9%). No patient experienced QTc prolongation >60 ms in the TASIGNA group.

Most frequently reported adverse drug reactions

Non-haematologic ADRs (excluding laboratory abnormalities) that were reported in at least 5% of the adult patients in any of the TASIGNA clinical studies that serve as a basis for the listed indications are shown in Table 7-1. These are ranked under heading of frequency, the most frequent first. Within each frequency grouping adverse drug reactions are presented in order of decreasing seriousness. In addition the corresponding frequency category for each adverse drug reaction is based on the following (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 7-1 Most frequently reported non-haematologic adverse drug reactions (≥5% in any TASIGNA group) [5,51,70,71,74,75,79,84,88,94,97,110]

			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 Drug 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	Very common	Rash	33	39	14	<1	3	2	28	1	2	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 Drug Reaction**	**N=279 %**	**N=277 %**	**N=280 %**	**N=279 %**	**N=277 %**	**N=280 %**	**N=458 %**	**N=458 %**	**N=321 %**	**N=137 %**
tissue disorders	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

			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 Drug Reaction**	**N=279 %**	**N=277 %**	**N=280 %**	**N=279 %**	**N=277 %**	**N=280 %**	**N=458 %**	**N=458 %**	**N=321 %**	**N=137 %**
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 adult 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 to <1/10; uncommon is ≥1/1,000 to <1/100; single events are captured as frequency not known) (Table 7-2). For laboratory abnormalities, very common events (≥1/10) not included in Table 7-1 are also reported. These adverse drug 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 [51,70,71,77,79,85,86,88,94,97,103,110].

Table 7-2 Adverse drug reactions reported in clinical studies in adult patients

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
Not known:	Sepsis, subcutaneous abscess, anal abscess, furuncle, tinea pedis, hepatitis B reactivation
Neoplasms Benign, Malignant and Unspecified	
Common:	Skin papilloma
Not known:	Oral papilloma, paraproteinaemia
Blood and lymphatic system disorders	
Common:	Leukopenia, eosinophilia, febrile neutropenia, pancytopenia, lymphopenia
Not known:	Thrombocythaemia, leukocytosis
Immune system disorders	
Not known:	Hypersensitivity
Endocrine disorders	
Uncommon:	Hyperthyroidism, hypothyroidism
Not known:	Hyperparathyroidism secondary, thyroiditis
Metabolism and nutrition disorders	
Very common:	Hypophosphataemia (including blood phosphorus decreased)
Common:	Electrolyte imbalance (including hypomagnesaemia, hyperkalaemia, hypokalaemia, hyponatraemia, hypocalcaemia, hypercalcaemia, hyperphosphataemia), diabetes mellitus, hyperglycaemia, hypercholesterolaemia, hyperlipidaemia, hypertriglyceridaemia
Uncommon:	Gout, dehydration, increased appetite, dyslipidaemia
Not known:	Hyperuricaemia, hypoglycaemia
Psychiatric disorders	
Common:	Depression, insomnia, anxiety
Not known:	Disorientation, confusional state, amnesia, dysphoria
Nervous system disorders	
Common:	Dizziness, peripheral neuropathy, hypoaesthesia, paraesthesia
Uncommon:	Intracranial haemorrhage, ischaemic stroke, transient ischaemic attack, cerebral infarction, migraine, loss of consciousness (including syncope), tremor, disturbance in attention, hyperaesthesia

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
Not known:	Papilloedema, diplopia, photophobia, eye swelling, blepharitis, eye pain, chorioretinopathy, conjunctivitis allergic, ocular surface disease
Ear and labyrinth disorders	
Common:	Vertigo
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
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
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
Not known:	Pulmonary hypertension, wheezing, oropharyngeal pain
Gastrointestinal disorders	
Common:	Pancreatitis, abdominal discomfort, abdominal distension, dyspepsia, dysgeusia, flatulence
Uncommon:	Gastrointestinal haemorrhage, melena, mouth ulceration, gastroesophageal reflux, stomatitis, oesophageal pain, dry mouth, gastritis, sensitivity of teeth
Not known:	Gastrointestinal ulcer perforation, retroperitoneal haemorrhage, haematemesis, gastric ulcer, oesophagitis ulcerative, subileus, enterocolitis, haemorrhoids, hiatus hernia, rectal haemorrhage, gingivitis
Hepatobiliary disorders	
Very Common:	Hyperbilirubinaemia (including blood bilirubin increased)
Common:	Hepatic function abnormal
Uncommon:	Hepatotoxicity, toxic hepatitis, jaundice
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

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
Not known:	Arthritis
Renal and urinary disorders	
Common:	Pollakiuria
Uncommon:	Dysuria, micturition urgency, nocturia
Not known:	Renal failure, hematuria, urinary incontinence, chromaturia
Reproductive system and breast disorders	
Uncommon:	Breast pain, gynaecomastia, erectile dysfunction
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)
Not known:	Localized oedema
Investigations	
Very common:	Alanine aminotransferase increased, aspartate amino-transferase 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
Not known:	Troponin increased, blood bilirubin unconjugated increased, blood insulin decreased, insulin C-peptide decreased, blood parathyroid hormone increased

Laboratory abnormalities

Clinically relevant or severe abnormalities of routine haematologic or biochemistry laboratory values in adult patients are presented in Table 7-3.

Table 7-3 Grade 3/4 Laboratory abnormalities [5,51,70,71,74,75,79,85,88,94,107]

	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**	**TASIGNA 400 mg twice daily CML-CP N=321**	**TASIGNA 400 mg twice daily 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	9%	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%
-Elevated Bilirubin (total)	4%	9%	<1%	7%	9%
-Elevated glucose	7%	7%	<1%	12%	6%
-Elevated Cholesterol (total)	0%	1%	0%	*	*
-Elevated tryiglycerides	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 adult Ph+ CML-CP patients who have achieved a sustained deep molecular response [115]

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 drug 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, facial paralysis [81,126].

Pediatric population

The safety of nilotinib in pediatric patients (from 2 to <18 years of age) with Ph+ CML-CP (n=69) has been investigated in two studies (see section 12 Clinical studies). In pediatric

patients, the frequency, type and severity of adverse drug reactions observed have been generally consistent with those observed in adults, with the exception of the laboratory abnormalities of hyperbilirubinaemia (Grade 3/4: 13.0%) and transaminase elevation (AST Grade 3/4: 1.4%, ALT Grade 3/4: 8.7%) which were reported at a higher frequency than in adult patients. Bilirubin and hepatic transaminase levels should be monitored during treatment (see section 4 Dosage regimen and administration) [120,121].

Growth retardation in pediatric population

In a Phase II (n=58) pediatric study, with a median exposure of 33 months in each cohort (newly diagnosed and resistant or intolerant Ph+ CML-CP), adverse drug reactions of mild and moderate severity associated with growth and deceleration of growth in regard to the height were reported in 3 patients (5.2%) including growth retardation in 2 adolescent patients and growth hormone deficiency with body height below normal in the remaining patient (age category: child). No negative effects were observed in relation to the bone age or bone biomarkers and no delayed puberty was observed. Close monitoring of growth in pediatric patients under TASIGNA treatment is recommended (see section 6 Warnings and precautions) [125].

8 Interactions

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 (P-gp) [7,8]. Therefore, absorption and subsequent elimination of systemically absorbed nilotinib may be influenced by drugs that affect CYP3A4 and/or P-gp.

Drugs that may increase nilotinib serum concentrations

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 P-gp. When the two drugs were administered concomitantly, the AUC of imatinib was increased by 18% to 39%, and the AUC of nilotinib was increased by 18% to 40% [60].

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 sections 4 Dosage regimen and administration and 6 Warnings and precautions regarding QT prolongation) [2]. 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% [53].

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 [2,53].

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 [64,65].

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 [91,92].

Drugs that may have their systemic concentration altered by nilotinib

In vitro nilotinib is identified as a competitive inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2D6 and UGT1A1, with Ki value being lowest for CYP2C9 (Ki=0.13 microM) [3,9,10]. 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 [104].

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 [62,63].

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 6 Warnings and precautions).

Food interactions

The absorption and the bioavailability of nilotinib are increased if it is taken with food, resulting in higher serum concentration (see sections 4 Dosage regimen and administration, 6 Warnings and precautions, and 11 Clinical pharmacology).

Grapefruit juice and other foods that are known to inhibit CYP3A4 should be avoided at any time [3].

9 Pregnancy, lactation, females and males of reproductive potential

9.1 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 it is used during pregnancy or if the patient becomes pregnant while taking TASIGNA, the patient must be informed of the potential risk to the fetus.

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 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 Dosage regimen and administration and 6 Warnings and precautions) [115].

Animal Data

Nilotinib did not induce teratogenicity, but did show embryo- and feto-toxicity at doses which also showed maternal toxicity. Increased post implantation loss was observed in both the fertility study, with treatment of both males and females, and in the embryo-toxicity study with the treatment of females. Embryo-lethality and fetal effects (mainly decreased fetal weights, visceral and skeletal variations) in rats and increased resorption of fetuses and skeletal variations in rabbits were present in the embryo-toxicity studies. Exposure to nilotinib in females at No-Observed-Adverse-Effect-Levels (NOAEL) was generally less or equal to that in humans at 800 mg/day [12,44-46].

In a pre- and postnatal study, the oral administration of nilotinib to female rats from day 6 of gestation to day 21 or 22 postpartum 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 NOAEL in maternal animals and offspring was a maternal dose of 20 mg/kg [56].

9.2 Lactation

Risk Summary

It is not known whether nilotinib is excreted in human milk. Studies in animals demonstrate that nilotinib 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 [11,124].

9.3 Females and males of reproductive potential

Contraception

Females

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 [102].

Infertility

The effect of nilotinib on male and female fertility is not known. In animal studies no effects on sperm count/motility, and on fertility were noted in male and female rats up to the highest tested dose of approximately 5-fold greater than the recommended dosage for humans [12].

10 Overdosage

Isolated reports of intentional overdose with nilotinib were reported, where an unspecified number of TASIGNA capsules were ingested in combination with alcohol and other drugs. Events included neutropenia, vomiting and drowsiness. No ECG changes or hepatotoxicity were reported. Outcomes were reported as recovered [67].

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

11 Clinical pharmacology

Pharmacotherapeutic group, ATC

Pharmacotherapeutic group: Antineoplastic agents – Protein-tyrosine kinase inhibitor.

ATC code: L01XE08.

Mechanism of action (MOA)

TASIGNA is a potent and selective [74] inhibitor of the ABL tyrosine kinase activity of the BCR-ABL oncoprotein both in cell lines and in primary Philadelphia-chromosome positive leukemia cells. The drug binds strongly within the ATP-binding site in such a manner that it is a potent inhibitor of wild-type BCR-ABL and maintains activity against 32/33 imatinib-resistant mutant forms of BCR-ABL. As a consequence of this biochemical activity, nilotinib selectively inhibits the proliferation and induces apoptosis in BCR-ABL dependent cell lines and in primary Philadelphia-chromosome positive leukemia cells derived from CML patients. In murine models of CML, as a single agent nilotinib reduces tumor 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 (CSF1R), discoidin domain receptor (DDR) [54,55,101] 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 11-1).

Table 11-1 Kinase profile of nilotinib (phosphorylation IC_{50} nM) [101]

BCR-ABL	PDGFR	KIT
20	69	210

Pharmacokinetics (PK)

Absorption

Peak concentrations of nilotinib are reached 3 hours after oral administration. Nilotinib absorption following oral administration was approximately 30% [4]. 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% [89]. In healthy volunteers, C_{max} and area under the 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 Dosage regimen and administration, section 6 Warnings and precautions and section 8 Interactions) [14]. Nilotinib absorption (relative bioavailability) may be reduced by approximately 48% and 22% in patients with total gastrectomy and partial gastrectomy, respectively [66].

Distribution

Blood-to-plasma ratio of nilotinib is 0.68. Plasma protein binding is approximately 98% on the basis of *in vitro* experiments [15,16].

Biotransformation/metabolism

Main metabolic pathways identified in healthy subjects are oxidation and hydroxylation. Nilotinib is the main circulating component in the serum, primarily metabolized by CYP3A4. None of the metabolites contribute significantly to the pharmacological activity of nilotinib [4].

Elimination

After a single dose of radiolabelled nilotinib in healthy subjects, greater than 90% of the dose was eliminated within 7 days mainly in feces. Parent drug accounted for 69% of the dose [4].

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 (%CV: 33% to 43%) [17].

Linearity/non-linearity

Steady-state nilotinib exposure was dose-dependent with less than dose-proportional increases in systemic exposure at dose levels higher than 400 mg given as once daily dosing. Daily systemic exposure to nilotinib of 400 mg twice-daily dosing at steady-state was 35% higher than with 800 mg once-daily dosing. Systemic exposure (AUC) of nilotinib at steady-state at a dose level of 400 mg twice daily was approximately 13.4% higher than with 300 mg twice daily. 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 [75]. There was no relevant increase in exposure to nilotinib when the dose was increased from 400 mg twice-daily to 600 mg twice-daily [17].

Steady-state conditions were essentially achieved by day 8. An increase in systemic exposure to nilotinib between the first dose and steady-state was approximately 2-fold for the 400 mg once daily dosing and 3.8-fold for the 400 mg twice-daily dosing.

Bioavailability/bioequivalence studies

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 [68].

Pediatric population

Following administration of nilotinib in pediatric patients at 230 mg/m^2 twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg), steady-state exposure and clearance of nilotinib were found to be similar (within 2-fold) to adult patients treated with 400 mg twice daily. The pharmacokinetic exposure of nilotinib following single or multiple doses appeared to be comparable between pediatric patients from 2 years to <10 years and from ≥10 years to <18 years [122].

12 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) [75].

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 [75].

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 [75,80,85,88,94,107].

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, 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 12-1 [75,74].

At the nilotinib recommended dose of 300 mg twice daily, the rates 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 rates 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 rates of MMR at 3, 6, 9 and 12 months were 0.7%, 12.0%, 18.0% and 22.3% [75].

The MMR rates at 12, 24, 36, 48, and 60 months are presented in Table 12-1.

Table 12-1 MMR rate [75,85,88,94,107]

	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.

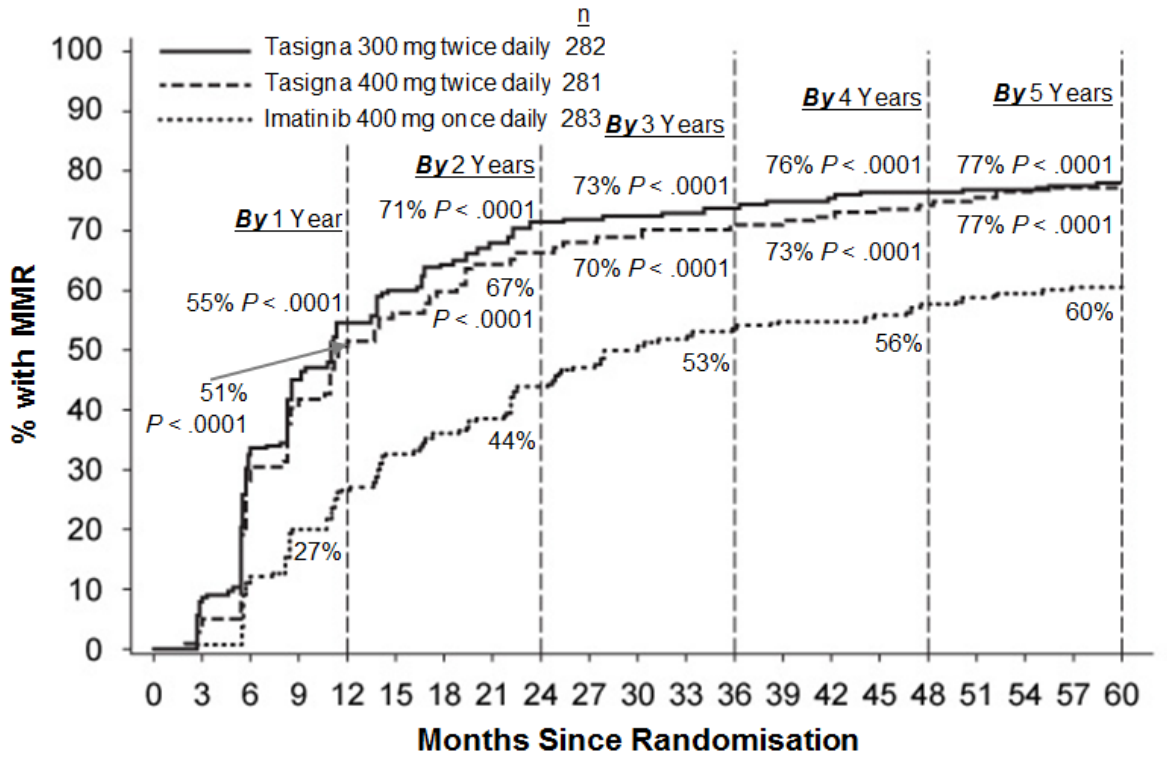
[2] Only patients who were in MMR at a specific time point are included as responders for that time point. A total of 199 (35.2%) of all patients were not evaluable for MMR at 36 months (87 in the nilotinib 300 mg BID group and 112 in the imatinib group) due to missing/unevaluable PCR assessments (n=17), 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 300 mg 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 12-1).

Figure 12-1 Cumulative Incidence of MMR [107]



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 [75,88,94,107].

In a retrospective analysis, 91% (234/258) of patients on nilotinib 300 mg twice daily achieved BCR-ABL levels ≤10% at 3 months of treatment compared to 67% (176/264) of patients on imatinib 400 mg once daily. Patients with BCR-ABL levels ≤10% at 3 months of treatment show a greater overall survival at 60 months compared to those who did not achieve this molecular response level (97% vs. 82% respectively [p=0.0116]) [95,108].

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 (hazard ratio/HR=2.20 and stratified log-rank p<0.0001 between nilotinib 300 mg twice daily and imatinib, HR=1.88 and stratified log-rank p<0.0001 between nilotinib 400 mg twice daily and imatinib) [94,107].

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 12-2 and the proportion of patients who had a molecular response of ≤0.01% and ≤0.0032% by IS-by different time points are presented in Figures 12-2 and 12-3. Molecular responses 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 12-2 Proportions of patients who had molecular response of ≤0.01% (4 log reduction and ≤0.0032% (4.5 log reduction) [88,94,107]

	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 12-2 Cumulative incidence of molecular response of ≤0.01% (4-log reduction) [107]

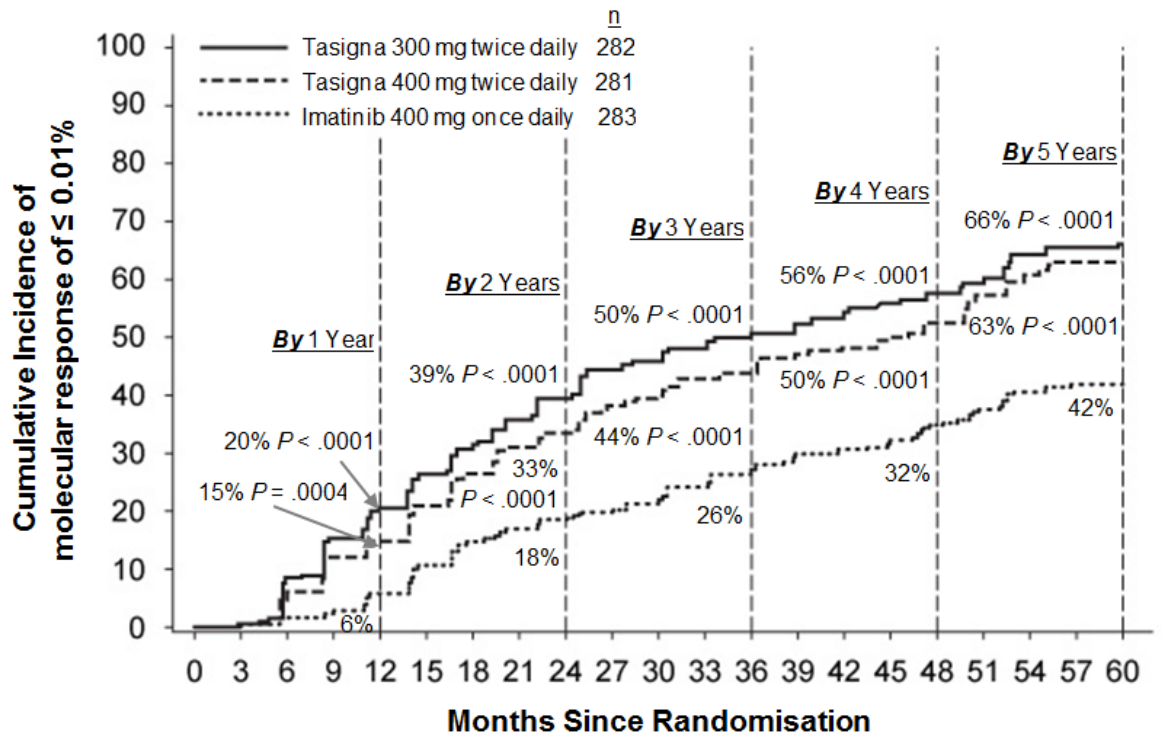
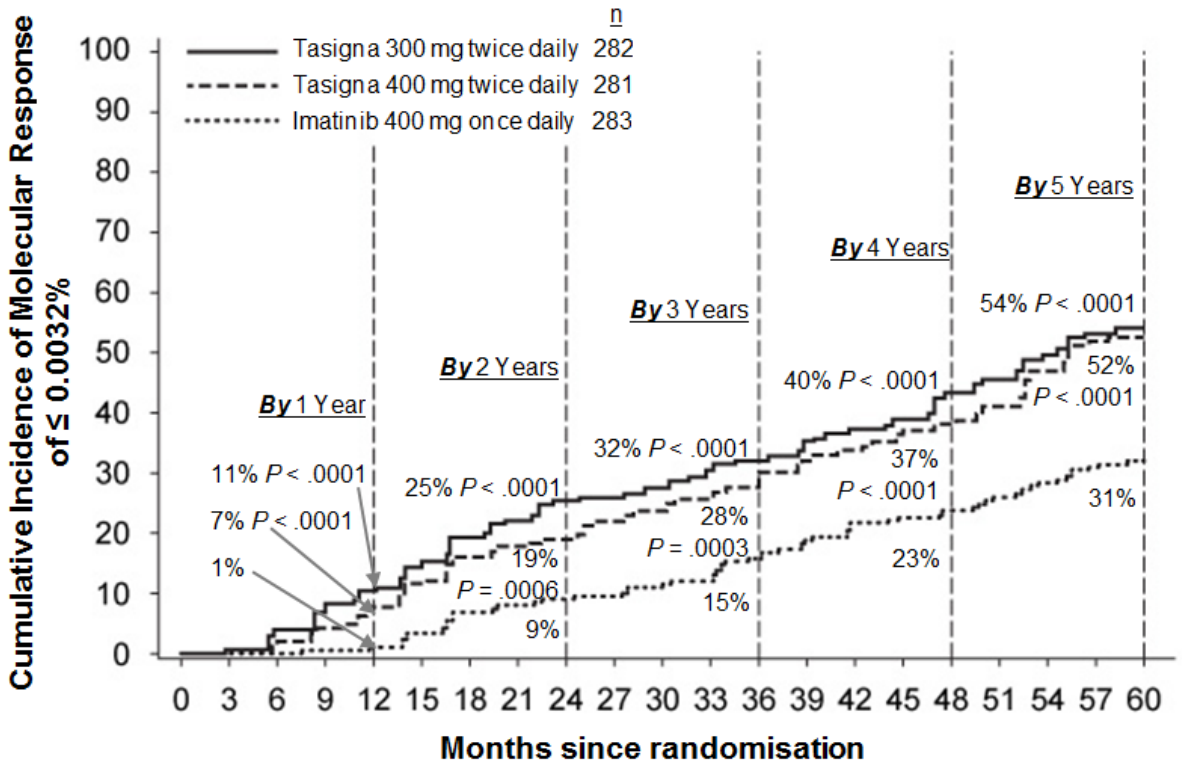


Figure 12-3 Cumulative incidence of molecular response of ≤0.0032% (4.5 log reduction) [107]



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% to 96.9%) in the nilotinib 300 mg twice daily group, 92.0% (95% CI: 88.2% to 95.8%) in the nilotinib 400 mg twice daily group and 89.1% (95% CI: 84.2% to 94.0%) in the imatinib 400 mg once daily group [85,94,107].

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 12-3.

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 12-3 CCyR rate [75,85]

	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% to 100%) in the nilotinib 300 mg twice daily group, 98.7% (95% CI: 97.1% to 100%) in the nilotinib 400 mg twice daily group and 97.0% (95% CI: 94.7% to 99.4%) in the imatinib 400 mg once daily group [85,94,107].

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 (b.i.d) and imatinib, HR=0.2457 and stratified log-rank p=0.0185 between nilotinib 400 mg b.i.d and imatinib) [75,80,85,88,94,107]. No new events of progression to AP/BC were reported on-treatment since the 2-year analysis.

Including clonal evolution as a criterion for progression, a total of 25 patients progressed to AP or BC on treatment by the cut-off date (3 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 b.i.d and imatinib, HR=0.2848 and stratified log-rank p=0.0085 between nilotinib 400 mg b.i.d and imatinib) [85,94,107].

Overall survival (OS) [80,85,88,94,107]

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).

Switch to TASIGNA treatment in adult patients with Ph+ CML-CP who have not achieved a molecular response greater than or equal to a 4.5-log reduction with imatinib treatment [118]

In an open-label, multicenter, randomized Phase III study, 207 adult patients with Ph+ CML-CP who received treatment with imatinib for at least 2 years, with no permanent imatinib dose adjustment within 6 months and no major toxicity within 3 months of study entry were enrolled in the study. Patients were randomized 1:1 either to receive TASIGNA 400 mg twice daily (n=104) or to continue treatment with imatinib at the same dose (400 mg or 600 mg once daily) as administered prior to randomization (n=103). Randomization was stratified by duration of prior treatment with imatinib and duration of prior interferon use. The median time on treatment (from first day of treatment to last day of randomized treatment) at cut-off was 47.2 months in the TASIGNA treatment arm, and 37.0 months and 26.7 months in the 400 mg and 600 mg dose cohorts of the imatinib arm, respectively.

The two treatment arms were well balanced with respect to demographic and baseline characteristics (including BCR-ABL transcript levels at study entry). Median age was 46 years in the TASIGNA arm and 52 years in the imatinib arm, with 13.5% and 13.6% of patients aged ≥65 years in the TASIGNA and imatinib treatment arms, respectively. There were more male (68.3% in the TASIGNA treatment arm and 63.1% in the imatinib treatment arm) than female patients. More than 80% of all patients were Caucasians. Up to the cut-off date, the median actual dose intensity was 775.7 mg/day in the TASIGNA treatment arm and 400 mg/day and 600 mg/day in the two dose cohorts of the imatinib treatment arm, respectively.

The primary endpoint of the study was the rate of confirmed best cumulative complete molecular response (CMR) within the first year of study therapy with TASIGNA or imatinib. The rate of confirmed best cumulative CMR during the first 12 months was 12.5% in the TASIGNA arm and 5.8% in the imatinib arm. The primary endpoint did not reach statistical significance at the early 12-month time point (p=0.1083), with an odds ratio (OR) of 2.096 in favor of TASIGNA.

Longer-term follow-up of the primary outcome variable at 48-months was a secondary endpoint. Analyses conducted to assess the achievement of different levels of molecular response up to crossover in patients without the corresponding response at baseline showed that switching from imatinib to TASIGNA was associated with a clinically meaningful increase in the numbers of patients attaining MMR, MR4.5, and CMR under their randomized treatment at Month 48 (see Table 12-4).

Table 12-4 Rate of best cumulative molecular response up to crossover by baseline molecular response status [118]

	TASIGNA N=104 n (%)	Imatinib N=103 n (%)
Number of patients with MMR at baseline	79 (76.0)	74 (71.8)
Number of patients without MMR at baseline	24 (23.1)	28 (27.2)
MMR by 12 months	18 (75.0)	10 (35.7)
MMR by 24 months	20 (83.3)	14 (50.0)
MMR by 36 months	21 (87.5)	15 (53.6)
MMR by 48 months	21 (87.5)	15 (53.6)
MR4.5 by 48 months	8 (33.3)	1 (3.6)
CMR by 48 months	7 (29.2)	1 (3.6)
Number of patients with MR4.5 at baseline	5 (4.8)	6 (5.8)
Number of patients without MR4.5 at baseline	98 (94.2)	96 (93.2)
MR4.5 by 12 months	32 (32.7)	13 (13.5)
MR4.5 by 24 months	42 (42.9)	20 (20.8)
MR4.5 by 36 months	46 (46.9)	25 (26.0)
MR4.5 by 48 months	51 (52.0)	27 (28.1)
CMR by 48 months	44 (44.9)	18 (18.8)
Number of patients with CMR at baseline	2 (1.9)	2 (1.9)
Number of patients without CMR at baseline	101 (97.1)	100 (97.1)
CMR by 12 months	21 (20.8)	10 (10.0)
CMR by 24 months	33 (32.7)	18 (18.0)
CMR by 36 months	41 (40.6)	20 (20.0)
CMR by 48 months	45 (44.6)	20 (20.0)

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 adult patients with imatinib resistant or intolerant CML with separate treatment arms for chronic and accelerated phase disease. 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 12-5). 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 [3,52,69].

Table 12-5 Duration of exposure with TASIGNA [3,52,69]

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

Resistance to imatinib included failure to achieve a complete hematologic 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 hematologic response. Imatinib intolerance included patients who discontinued imatinib because of toxicity and were not in major cytogenetic response at time of study entry [3].

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 12-6). 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 [52].

Table 12-6 CML disease history characteristics [3,13,52,69]

	Chronic Phase (n = 321)	Accelerated Phase (n = 137)*
Median time since diagnosis in months (range)	58 (5 to 275)	71 (2 to 298)
Imatinib		
Resistant	226 (70%)	109 (80%)
Intolerant without MCyR	95 (30%)	27 (20%)
Median time of imatinib treatment in days (25^{th} to 75^{th} percentiles)	976 (519 to 1,488)	857 (424 to 1,497)
Prior hydroxyurea	83%	91%
Prior Interferon	58%	50%
Prior organ transplant	7%	8%

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

The primary endpoint in the CP patients was major cytogenetic response (MCyR), defined as elimination (CCyR, complete cytogenetic response) or significant reduction to <35% Ph+ metaphases (partial cytogenetic response) of Ph+ hematopoietic cells. Complete hematologic response in CP patients was evaluated as a secondary endpoint. The primary endpoint in the AP patients was overall confirmed hematologic response, defined as either a complete hematologic response, no evidence of leukemia or return to chronic phase [3].

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 CCyR rate was 44%. The median time to achieve CCyR was just past 3 months (median 3.3 months). Of the patients who achieved MCyR, 77% (95% CI: 71% to 84%) were maintaining response at 24 months. Median duration of MCyR has not been reached. Of the patients who achieved CCyR, 84% (95% CI: 77% to 91%) were maintaining response at 24 months. Median duration of CCyR has not been reached. Patients with a CHR at baseline achieved a MCyR faster (1.4 vs. 2.8 months). Of CP patients without a baseline CHR, 76% achieved a CHR, median time to CHR was 1 month and median duration of CHR has not been reached [3,52,70].

The estimated 24-month overall survival rate in CML-CP patients was 87% [70].

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% to 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 12-7 [13,52,71].

The estimated 24-month overall survival rate in CML-AP patients was 70% [71].

Table 12-7 Response rate in CML [3,52,70,71]

(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)
Hematologic Response (%)						
Overall (95%CI)	-	-	-	56 (35-75)	55 (45-65)	55 (47-64)
Complete						
NEL	90 (79-97)	72 (64-79)	76[1] (70-82)	37	30	31
Return to CP	-	-	-	15	11	12
	-	-	-	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 leukemia/marrow response

[1]- 114 CP patients had a CHR at baseline and were therefore not assessable for complete hematologic 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. 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 [1].

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 [52].

Treatment discontinuation in newly diagnosed Ph+ CML-CP adult patients who have achieved a sustained deep molecular response [116]

In an open-label, multicenter, 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). Of the 215 patients, 190 patients (88.4%) entered the 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 MR4.0 (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 MR4.0 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 600.0 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.

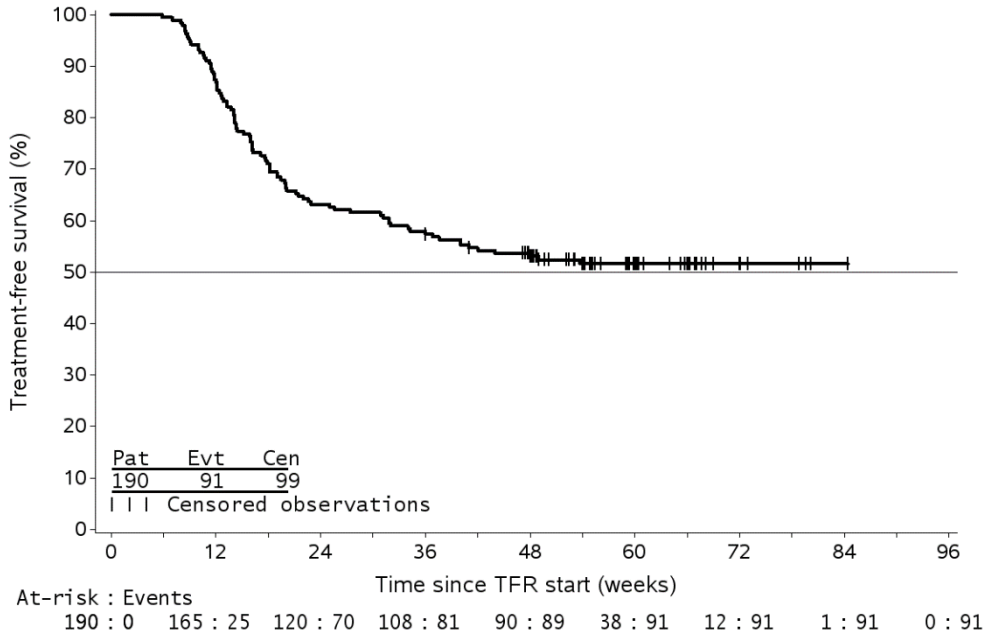
Eighty-eight patients (46.3%) discontinued from the TFR phase due to loss of MMR, and 1 (0.5%), 1 (0.5%), and 3 patients (1.6%) due to death from unknown cause, physician decision, and subject decision, respectively. Among the 88 patients who discontinued the TFR phase due to loss of MMR, 86 patients 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.

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 12-4).

Figure 12-4 Kaplan-Meier estimate of treatment-free survival after start of TFR (Full Analysis Set)



Treatment discontinuation in Ph+ CML-CP adult patients who have achieved a sustained deep molecular response on TASIGNA following prior imatinib therapy [117]

In an open-label, multicenter, 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 $\leq$ 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.

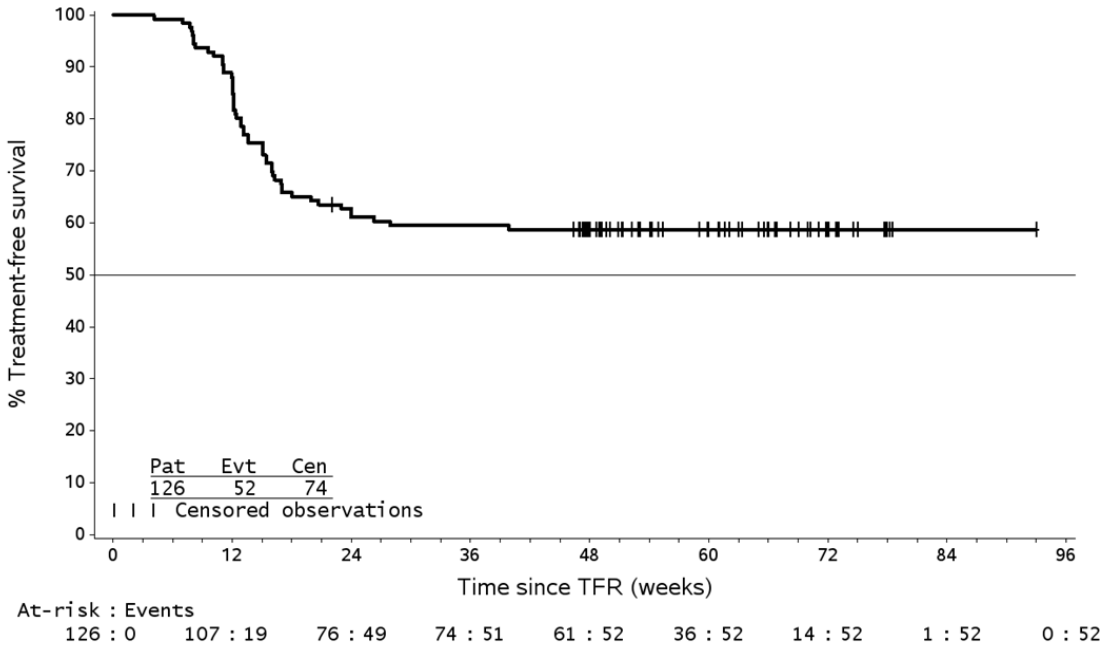
The primary endpoint was defined as the proportion of patients without confirmed loss of MR4.0 or loss of MMR within 48 weeks following discontinuation of TASIGNA therapy. Of the 126 patients who entered the TFR phase, 73 patients (57.9%, [95% CI: 48.8, 66.7]) had no loss of MMR, no confirmed loss of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

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 12-5).

Figure 12-5 Kaplan-Meier estimate of treatment-free survival after start of TFR (Full Analysis Set)



Pediatric patients with newly diagnosed Ph+ CML-CP or resistant or intolerant Ph+ CML-CP [120,121]

The safety and efficacy of nilotinib in pediatric patients with Ph+ CML-CP have been investigated in two studies [122,123]. A total of 69 pediatric patients (from 2 to <18 years of age) with either newly diagnosed Ph+ CML-CP (n=25) or imatinib/dasatinib resistant or imatinib-intolerant Ph+ CML-CP (n=44) received nilotinib treatment at a dose of 230 mg/m^2 twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg).

In the pooled CML patient population, the median actual dose intensity was 435.5 mg/m^2/day (range: 149 to 517 mg/m^2/day), and the median relative dose intensity was 94.7% (range: 32 to 112%). Forty patients (58.0%) had relative dose intensity superior to 90%. The median time on treatment with nilotinib was 13.80 months (range: 0.7 to 30.9 months).

In the resistant or intolerant CML patients, the major molecular response (MMR; BCR-ABL/ABL ≤0.1% IS) rate was 40.9% (95% CI: 26.3, 56.8) at 12 cycles, with 18 patients being in MMR. In the newly diagnosed CML patients, the MMR rate was 60.0% (95% CI: 38.7, 78.9) at 12 cycles, with 15 patients achieving MMR. In resistant or intolerant CML patients, the cumulative MMR rate was 47.7% by cycle 12. In newly diagnosed CML patients, the cumulative MMR rate was 64.0% by cycle 12.

Among the 21 resistant or intolerant CML patients who were in MMR at any time on treatment, the median time to first MMR was 2.76 months (95% CI: 0.03, 5.55). For the 17 newly diagnosed CML patients who achieved MMR, the median time to first MMR was 5.55 months (95% CI: 5.52, 5.75).

Among resistant or intolerant CML patients, the percentage of patients who achieved BCR-ABL/ABL ≤0.01% IS (MR4.0) by the cut-off date was 11.4%, while 4.5% of the patients achieved BCR-ABL/ABL ≤0.0032% IS (MR4.5). Among newly diagnosed patients, the percentage of patients who achieved MR4.0 was 32%, while 28.0% achieved MR4.5.

None of the 21 resistant or intolerant CML patients who were in MMR on treatment, had confirmed loss of MMR. Among the 17 newly diagnosed CML patients who achieved MMR, one patient had confirmed loss of MMR (the patient lost CHR due to an increase in basophil count, however, did not progress to AP/BC).

One resistant or intolerant CML patient progressed to AP/BC after about 10 months on treatment.

No deaths were reported on treatment or after treatment discontinuation in both studies.

13 Non-clinical safety data

Nilotinib has been evaluated in safety pharmacology, repeated dose toxicity, genotoxicity, reproductive toxicity (see section 9 Pregnancy, lactation, females and males of reproductive potential), 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 [18]. *In vitro* cardiac safety studies demonstrated a preclinical signal for QT prolongation [19,20]. No effects were seen in ECG measurements in dogs or monkeys treated up to 39 weeks [21,22] or in a special telemetry study in dogs [23].

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 [24-35].

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 [36-43]. In the 2-year rat carcinogenicity study there was no evidence of carcinogenicity upon administration of nilotinib at 5, 15 and 40 mg/kg/day. Exposures (in terms of AUC) at the highest dose level were representing approximately 2 to 3 times human daily steady-state exposure (based on AUC) to nilotinib at the dose of 800 mg/day. The major target

organ for non-neoplastic lesions was the uterus (dilatation, vascular ectasia, hyperplasia endothelial cell, inflammation and/or epithelial hyperplasia) [82,83,90].

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) [112,113].

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 [72].

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 [47-50].

14 Pharmaceutical information

Incompatibilities

Not applicable.

Special precautions for storage

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

Do not store above 25°C/30°C [Country specific].

Store in the original package.

Information might differ in some countries.

Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

15 References

		Module	Vol.	Section/ Page
1.	Summary of Clinical Efficacy	2	3	2.7.3/1
2.	Clinical Overview	2	1	2.5/1
3.	Study 2101E2 (Study 2101 CP CSR) Study 2101 (Phase II component, imatinib-resistant/intolerant CML-chronic phase): A Phase IA/II, multicenter, dose-escalation study of oral AMN107 on a continuous daily dosing schedule in adult patients with Gleevec® (imatinib)-resistant/intolerant CML in chronic or accelerated phase or blast crisis, relapsed/refractory Ph+ALL, and other hematologic malignancies	5	57	5.3.5.2/ 17782
4.	CAMN107A2104 (ADME study) An open-label, single center study to determine the absorption, metabolism, and excretion (AME) of AMN107 after a single oral administration of 400 mg 100µCi [14C] AMN107 in male HV	5	1	5.3.2.2/1
5.	Summary of Clinical Safety	2	3	2.7.4/1
6.	Study 2119 CSR A randomized, blinded, placebo and active controlled study to evaluate the cardiac safety of multiple doses of AMN107 in HV	5	14	5.3.4.1/1
7.	Summary of Clinical Pharmacology	2	3	2.7.2/1
8.	ADME(US) R0301031: 3HAMN107 *In vitro* permeability assessment and transporter interactions across Caco-2 cell monolayers.	4	6	4.2.2.6/ 421
9.	DMPK R0301332: Cytochrome P450 enzyme inhibition kinetics of NVP-AMN107	4	5	4.2.2.6/ 30
10.	DMPK R0500591: *In vitro* assessment of UTG1A1 inhibition by NVP-AMN107	4	6	4.2.2.6/ 467
11.	DMPK R0600046: Excretion in milk after a single oral dose of 14CAMN107 in the rat.	4	4	4.2.2.3/ 105
12.	Study no. 0570152. An oral (gavage) fertility and early embryonic development study in rats.. Novartis Pharmaceuticals Corporation. New Jersey, USA. 02 Jun 06.	4	19	4.2.3.5.1/1
13.	Study 2101E1 (Study 2101 AP CSR) Study 2101 (Phase II component, imatinib-resistant/intolerant CML-accelerated phase): A Phase IA/II, multicenter, dose-escalation study of oral AMN107 on a continuous daily dosing schedule in adult patients with Gleevec® (imatinib)-resistant/intolerant CML in chronic or accelerated phase or blast crisis, relapsed/refractory Ph+ALL, and other hematologic malignancies	5	97	5.3.5.2/ 35666

14.	CAMN107A2106 Phase I PK An open label, randomized, three period crossover, single center study to determine the effect of food on the pharmacokinetics of a single 400 mg oral dose of AMN107 in healthy subjects under both fasting and fed conditions	5	10	5.3.3.4/1
15.	ADME(US) R0301031: 3HAMN107 *In vitro* permeability assessment and transporter interactions across Caco-2 cell monolayers	4	4	4.2.2.6/ 421
16.	DMPK R0400674: In vitro protein binding of 3HAMN107 in human albumin and α1-acid glycoprotein.	4	4	4.2.2.3/ 37
17.	CAMN107A2101 Phase I PK Study 2101 (Clinical Pharmacology Report for the Phase IA component): A Phase IA/II, multicenter, dose-escalation study of oral AMN107 on a continuous daily dosing schedule in adult patients with Gleevec® (imatinib)-resistant/intolerant CML in chronic or accelerated phase or blast crisis, relapsed/refractory Ph+ALL, and other hematologic malignancies	5	8	5.3.3.2/1
18.	Study no. 0510047. An oral safety pharmacology study in rats (nervous and respiratory system). Novartis Pharma AG. Basel, Switzerland. 19 Sep 05.	4	2	4.2.1.3/ 347
19.	Study no. 0380166. Effects of AMN107 on cloned hERG channels expressed in mammalian cells. Chan Test Inc. Cleveland, USA. 29 Jan 04.	4	1	4.2.1.3/ 67
20.	Study no. 0350152. Electrophysiological investigations in the isolated rabbit heart. Novartis Pharma AG. Basel, Switzerland. 23 Dec 03.	4	1	4.2.1.3/ 90
21.	Study no. 0370146. 4-week oral (gavage) dose toxicity study in rats with a 4-week recovery period. Novartis Pharmaceuticals Corporation. New Jersey, USA. 27 Mar 04.	4	9	4.2.3.2/ 965
22.	Study no. 0580157. A 39-week oral (gavage) toxicity study in cynomolgus monkeys with a 4-week recovery period.. SNBL USA Ltd. Everett, Washington, USA. 07 Jul 06.	4	15	4.2.3.2/ 3476
23.	Study no. 0380165. CTBR. A pharmacological assessment of the oral (gavage) administration of AMN107 on the cardiovascular system of the conscious telemetered male beagle dog. Senneville, Quebec, Canada. 16 Apr 04.	4	2	4.2.1.3/ 474
24.	Study no. 02R143. Tolerability in the mouse by the oral route. Novartis Pharma AG. Basel, Switzerland. 19 Dec 03.	4	6	4.2.3.2/1
25.	Study no. 0580231. A 4-week oral (feed) dose range-finding toxicity study of AMN107 in the mouse. Charles River Laboratories. Senneville, Quebec, Canada. 05 Jun 06.	4	7	4.2.3.2/9

26.	Study no. 0370053. An oral (gavage) rising dose toxicity study in rats. Novartis Pharmaceuticals Corporation. New Jersey, USA. 21 May 03.	4	8	4.2.3.2/ 457
27.	Study no. 0370138. 2-week oral (gavage) dose range-finding toxicity study in rats. Novartis Pharmaceuticals Corporation. New Jersey, USA. 19 Jan 04.	4	8	4.2.3.2/ 496
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29.	Study no. 0510076. 4-week oral toxicity study in rats with impurities. Novartis Pharma AG. Basel, Switzerland. 10 Mar 06.	4	10	4.2.3.2/ 1211
30.	Study no. 0580158. A 26-week oral (gavage) toxicity study in rats with a 4-week recovery period. SNBL USA Ltd. Everett, Washington, USA. 20 Jul 06.	4	1 1	4.2.3.2/ 1566
31.	Study no. 0370052. An oral (gavage) rising dose toxicity study in dogs. Novartis Pharmaceuticals Corporation. New Jersey, USA. 10 Jun 03.	4	14	4.2.3.2/ 2892
32.	Study no. 0370139. 2-week oral (gavage) dose range-finding toxicity study in dogs. Novartis Pharmaceuticals Corporation. New Jersey, USA. 16 Mar 04.	4	14	4.2.3.2/ 2934
33.	Study no. 0370147. 4-week oral (gavage) toxicity study in dogs with a 4-week recovery period. Novartis Pharmaceuticals Corporation. New Jersey, USA. 21 Apr 04.	4	14	4.2.3.2/ 3035
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43.	Study no. 0512401. Oral bone marrow micronucleus test in rats. Novartis Pharma AG. Basel, Switzerland. 12 May 05.	4	19	4.2.3.3.2/ 1
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45.	Study no. 0570056. An oral embryo-fetal development dose range-finding study in rabbits. Novartis Pharmaceuticals Corporation. New Jersey, USA. 22 Dec 05.	4	21	4.2.3.5.2/ 195
46.	Study no. 0570058. An oral embryo-fetal development study in rabbits. Novartis Pharmaceuticals Corporation. New Jersey, USA. 20 Jan 06.	4	21	4.2.3.5.2/ 334
47.	Study no. 0517003. UV/vis absorption spectrum for initial phototoxicity assessment. Novartis Pharma AG. Basel, Switzerland. 23 Mar 05.	4	22	4.2.3.7.7/ 1
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Newly added references BPI amendment 31 March 2010

73. 2.3 Quality Overall Summary Drug Product - Description and Composition of the Drug Product (AMN107). 150 mg Hard Capsules. 6002441_23P_M_840_1. Description and composition of drug product/6002441_P1_M_975_1. Novartis Pharma AG. Basel, Switzerland. 05 Nov 09.

74. 2.5 Clinical Overview (AMN107). Treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukemia in chronic phase (Ph+ CML-CP). Novartis Pharma AG. Basel, Switzerland. 07 Dec 09.

75. CAMN107A2303 - A phase III multi-center, open-label, randomized study of imatinib versus nilotinib in adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia in chronic phase (CML-CP). Full Clinical Study Report (12 month primary analysis). Novartis Pharma AG. Basel, Switzerland. 26 Nov 09.

76. 2.7.3 Summary of Clinical Efficacy (AMN107). Treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukemia in chronic phase (Ph+ CML-CP). Novartis Pharma AG. Basel, Switzerland. 27 Nov 09.

77. 2.7.4 Summary of Clinical Safety (AMN107). Treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukemia in chronic phase (Ph+ CML-CP). Novartis Pharma AG. Basel, Switzerland. 06 Dec 09.

78. 2.3 Quality Overall Summary Drug Product - Stability summary and conclusion (AMN107). 150 mg Hard Capsules. 6002441_23P_M_840_1. Stability summary and conclusion/6002441_P81_M_840_1. Novartis Pharma AG. Basel, Switzerland. 05 Nov 09.

79. 2.7.4 Summary of Clinical Safety Update (AMN107). Treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukemia in chronic phase (Ph+ CML-CP). Novartis Pharma AG. Basel, Switzerland. 24 Mar 10.

80. 2.7.3 Summary of Clinical Efficacy Update (AMN107). Treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukemia in chronic phase (Ph+ CML-CP). Novartis Pharma AG. Basel, Switzerland. 23 Mar 10.

Newly added references BPI amendment 24 November 2010

81. 2.5 Clinical Overview Rationale for changes to Core Data Sheet (CDS)/Product Information-Tumor Lysis Syndrome , Novartis Pharma AG. 24 Nov 10.

Newly added references BPI amendment 06 December 2010

82. Study no. 0670450. A 2-year oral (feed) carcinogenicity study in rat with a 1-year interim necropsy. Charles River Laboratories. Senneville, Quebec, Canada (Study no. 801831), 26 Nov 10.

83. Nonclinical Overview - Rationale for changes to Core Data Sheet (CDS) / Product Information – Non-clinical safety data for rat carcinogenicity. Novartis Pharma AG. Basel, Switzerland. 29 Nov 10.

Newly added references BPI amendment 4 February 2011

84. 2.5 Clinical Overview (AMN107). Treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukemia in chronic phase (Ph+ CML-CP). Novartis Pharma AG. Basel, Switzerland. 10 Jan 11.

85. CAMN107A2303 - A phase III multi-center, open-label, randomized study of imatinib versus nilotinib in adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia in chronic phase (CML-CP). Full Clinical Study Report (24 months update). Novartis Pharma AG. Basel, Switzerland. 13 Jan 11.

Newly added references BPI amendment 19 May 2011

86. 2.5 Clinical Overview (AMN107). Rationale for changes to Core Data Sheet (CDS) / Product Information – Peripheral Arterial Occlusive Disease. Novartis. 5 May 11.

Newly added references BPI amendment 2 March 2012

87. 2.5 Clinical Overview (AMN107). Treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukemia in chronic phase (Ph+ CML-CP). Novartis. Switzerland. 17 Feb 12.

88. CAMN107A2303 - A phase III multi-center, open-label, randomized study of imatinib versus nilotinib in adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia in chronic phase (CML-CP). Full Clinical Study Report (36 months update). Novartis. Switzerland. 8 Feb 12.

89. CAMN107A2129 - A randomized, open label, two-period crossover study evaluating the relative bioavailability of nilotinib/Tasigna® capsule formulation (final market image 200 mg strength) in comparison to an oral drink solution in healthy subjects. Study Report AMN107A2129. 29 Nov 10.

90. 2.4 Nonclinical Overview - Rationale for changes to Core Data Sheet (CDS) / Product Information – Non-clinical safety data for rat carcinogenicity. Amendment no.1 Novartis. Switzerland. 21 Sep 11.

Newly added references BPI amendment 27 July 2012

91. 2.5 Clinical Overview - Rationale for changes to Core Data Sheet (CDS) / Product Information - Concomitant use of H2-blocker or antacid with nilotinib. Novartis. 21 Switzerland. 21 Jun 12.

92. CAMN107A2131 - A four-way crossover, randomized open-label study to evaluate the effects of two gastric pH-elevating agents, famotidine (given 10 hours before and 2 hours after nilotinib) and an antacid preparation (given 2 hours before or after nilotinib), on the pharmacokinetics of nilotinib in healthy subjects. Study Report AMN107A2131. Novartis. Switzerland. 25 May 12.

Newly added references BPI amendment 18 April 2013

93. 2.5 Clinical Overview (AMN107). Treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukemia in chronic phase (Ph+ CML-CP) – 48 month update. Novartis. Switzerland. 21 Feb 13.

94. CAMN107A2303 - A phase III multi-center, open-label, randomized study of imatinib versus nilotinib in adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia in chronic phase (CML-CP). Full Clinical Study Report (48 months update). Novartis. Switzerland. Feb 13.

95. AMN107A2303 BCR-ABL transcript levels of >10% after 3 months of nilotinib or imatinib treatment are predictive of poor outcomes in newly diagnosed chronic myeloid leukemia patients in chronic phase: landmark analysis of the ENESTnd 4-year data. Landmark analysis of ENESTnd 4-year data. Novartis. Switzerland. Feb 13.

96. 2.7.4 Summary of Clinical Safety Update (AMN107). Treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukemia in chronic phase (Ph+ CML-CP) – 48 month update. Novartis. Switzerland. 07 Feb 13.

97. 2.5 Clinical Overview - Rationale for changes to Tasigna Core Data Sheet, section: Adverse drug Reactions. Novartis. Switzerland. 07 Mar 13.

98. 2.5 Clinical Overview - Rationale for changes to Novartis BPI/CDS Sections: Posology and method of administration and Special warnings and precautions.13 Mar 13.

Newly added references CDS update v1.0 – 31-Jul-2013

99. 2.5 Clinical Overview-Rationale for changes to Core Data Sheet (CDS) Sections 4 and 6: Dosage and administration and Warnings and precautions. (Glucose). Novartis. Switzerland. 30 May 13.

100. 2.5 Clinical Overview - Rationale for changes to Core Data Sheet (CDS)/Product Information- Section 8 Interactions. Novartis. Switzerland. 12 Jul 13.

101. [Manley PW, Drueckes P, Fendrich G, el al (2010)] Extended kinase profile and properties of the protein kinase inhibitor Nilotinib. Biochim Biphys Acta; 1804:445-53.

102. 2.5 Clinical Overview - Rationale for changes to Core Data Sheet (CDS)/ Section 9 Women of child-bearing potential, pregnancy, breast-feeding and fertility. Novartis. Switzerland. 12 Jul 13.

Newly added reference CDS amendment v1.1 – 17-Jan-2014

103. 2.5 Clinical Overview-Rationale for changes to Core Data Sheet (CDS) Sections 6 and 7: Warnings and precautions. (CVEs) and Adverse drug reactions. Novartis. Switzerland. Dec 13.

Newly added references CDS amendment v1.2– 24-Apr-2014

104. 2.5 Clinical Overview - Rationale for changes to the Novartis CDS, section 8 Interactions - concerning concomitant use of midazolam or sensitive CYP3A4 substrates with nilotinib. Novartis. Switzerland. 06 Mar 14.

105. 2.5 Clinical Overview-Rationale for changes to the Tasigna CDS Section 6: Warnings and precautions - Fluid Retention. Novartis. Switzerland. 23 Apr 14.

Newly added reference CDS amendment v1.3– 6-May-2014

106. 2.5 Clinical Overview (AMN107). Treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukemia in chronic phase (Ph+ CML-CP) – 60 month update. Novartis. Switzerland. Feb 14.

107. CAMN107A2303 - A phase III multi-center, open-label, randomized study of imatinib versus nilotinib in adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia in chronic phase (CML-CP). Full Clinical Study Report (60 months update). Novartis. Switzerland. Feb 14.

108. AMN107A2303 BCR-ABL transcript levels of >10% after 3 months of nilotinib or imatinib treatment are predictive of poor outcomes in newly diagnosed chronic myeloid leukemia patients in chronic phase: landmark analysis of the ENESTnd 5-year data. Landmark analysis of ENESTnd 5-year data. Novartis. Switzerland. Feb 14.

109. 2.7.4 Summary of Clinical Safety Update (AMN107). Treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukemia in chronic phase (Ph+ CML-CP) – 60 month update. Novartis. Switzerland. Feb 14.

110. 2.5 Clinical Overview - Rationale for changes to Tasigna Core Data Sheet, sections 4,6,7: Dosage and administration, Warnings and precautions, Adverse drug reactions. Novartis. Switzerland. Mar 14.

Newly added reference CDS amendment v1.4 – 25-Jul-2014

111. 2.5 Clinical Overview (AMN107). Rationale for changes to Core Data Sheet (CDS) – Inclusion of molecular response monitoring for Ph+ CML patients. Novartis. 15 Jul 14.

Newly added references CDS amendment v1.5 – 13-Apr-2015

112. 2.4 Nonclinical Overview (AMN107). Rationale for changes to Core Data Sheet (CDS) / Product Information – Nonclinical safety data for mouse carcinogenicity. Novartis. Switzerland. 25-Mar-2015.

113. Study No. 1270142. 26-Week Oral Gavage Carcinogenicity and Toxicokinetic Study with AMN107 in 001178-T (Hemizygous) RasH2 Mice. Covance Laboratories Inc. Madison, Wisconsin (Study no. 8285128). Mar-2015.

Newly added reference CDS amendment v1.6 – 23-Mar-2016

114. 2.5 Clinical Overview (AMN107). Rationale for changes to Core Data Sheet (CDS) / Product Information – Signal of Hepatitis B virus Reactivation for Bcr-Abl Tyrosine Kinase Inhibitors: Tasigna. Novartis. Mar-2016.

Newly added references CDS amendment v1.7 –15-Jul-2016

115. 2.5 Clinical Overview (AMN107). BCR-ABL1 positive chronic myelogenous leukemia in chronic phase (treatment discontinuation). Novartis. Switzerland. Jun-2016.

116. Study CAMN107I2201 - A single-arm, multicenter, nilotinib treatment-free remission study in patients with BCR-ABL1 positive Chronic Myelogenous Leukemia in chronic phase who have achieved durable minimal residual disease (MRD) status on first line nilotinib treatment. Full Clinical Study Report (TFR 48 weeks). Novartis. Switzerland. 31-May-2016.

117. CAMN107A2408 - A Phase II, single arm, open label study of treatment-free remission in Chronic Myeloid Leukemia (CML) chronic phase (CP) patients after achieving sustained MR4.5 on nilotinib. Full Clinical Study Report (TFR 48 weeks). Novartis. Switzerland. May-2016.

118. Study CAMN107A2405 - An open label, randomized study of nilotinib vs. standard imatinib (400/600 mg qd) comparing the kinetics of complete molecular response for CML-CP patients with evidence of persistent leukemia by RQ-PCR – Month 48 interim analysis. Full Clinical Study Report. Novartis. Switzerland. 31-May-2016.

Newly added references CDS amendment v1.8 - 05-Dec-2016

119. 2.3 Quality Overall Summary Drug Product – Tasigna (AMN107) 50 mg Hard Capsules. Description and composition of drug product (6001342_23P_M_966_1). Novartis. 26-Sep-2016.

120. 2.5 Clinical Overview in Pediatric Patients with Chronic Myeloid Leukemia. Novartis. 06-Oct-2016.

121. 2.7.4 Summary of Clinical Safety in Pediatric Patients with Chronic Myeloid Leukemia. Novartis. 05-Oct-2016.

122. Study CAMN107A2120 - A multi-center, open-label, pharmacokinetic study of oral nilotinib in pediatric patients with newly diagnosed chronic phase (CP) Ph+ CML, with CP or accelerated phase (AP) Ph+ CML resistant/intolerant to imatinib and/or dasatinib, or with refractory/relapsed Ph+ ALL. Full Clinical Study Report. Novartis. 26-Nov-2015.

123. Study CAMN107A2203 - A multi-center, open label, non-controlled phase II study to evaluate efficacy and safety of oral nilotinib in pediatric patients with newly diagnosed Ph+ chronic myelogenous leukemia (CML) in chronic phase (CP) or with Ph+ CML in CP or accelerated phase (AP) resistant or intolerant to either imatinib or dasatinib – 12-month analysis. Full Clinical Study Report. Novartis. 15-Sep-2016.

Newly added reference CDS update v2.0 – 30-Jan-2018

124. 2.5 Clinical Overview Rationale for changes to Core Data Sheet (CDS) / Product Information – Section 9 Pregnancy, lactation, and females and males of reproductive potential. Novartis. Jan-2018.

Newly added reference CDS update v2.1 – 25-Mar-2019

125. 2.5 Clinical Overview Rationale for changes to Core Data Sheet (CDS) / Product Information –Growth Retardation. Novartis. Mar-2019.

Newly added reference CDS amendment v2.2 – 18-May-2020

126. 2.5 Clinical Overview Rationale for changes to Core Data Sheet (CDS) / Product Information – Facial paralysis. Novartis. Apr-2020.

16 CDS history table

Version	Effective date	GLC/PSB approval date	SLC Tracking No.	Section keyword	Refs.	Author(s) GLM/GPRD/ GPRM
BPI creation	13-Oct-2006	18-Sep-2006	N/A	CDS Creation	1-50	Laura Grazioli, Robert Miranda Joseph Quintavalla Sandra Jullian, DRA Senior GL Manager
BPI amendment 1	11-Apr-2007	8-Mar-2007	2007-PSB/GLC-0070-s	Amend - Safety and efficacy based on the 120-day update	51-52	Joseph Quintavalla, DRA TA Manager; Robert Miranda, DRA Project Team Rep.; Sabina Hernandez Penna, DRA Global Labelling
BPI amendment 2	11-Jul-2008	08-Apr-2008 17-Jun-2008 14-Jul-2008	2008-PSB/GLC-0132-s	Amend - Additional data from the studies: AMN107A2115, DMPK, R0500591 and 901168. Data from completed hepatic impairment study 2116 Data from study 2103 regarding Pgp interactions. Editorial revisions to be consistent with BPI template and/or add clarity.	53-61	Robert Miranda, DRA Project Team Rep; Sabina Hernandez Penna, DRA Global Labelling
BPI amendment 3	08-May-2009	17-Feb-2009 21-Apr-2009	2009-PSB/GLC-0182-s	Amend to include a precautionary statement for the reduced bioavailability in patients with total gastrectomy. Amend to reflect the results of the DDI studies CAMN107A2123 (warfarin) and CAMN107A2121 (PPI). Amend to clarify that, to date, no “adequate” data are available on the use of Tasigna in pregnant woman. Amend to include also the term “myelosuppression” for completeness. Amend to include information on intentional overdose cases as discussed in PSUR 3. Amend to include PK results for the reduced bioavailability in patients with total and partial gastrectomy.	62-67	Anne-Marie Dujardin, Sr. DRA Manager, OBU Sabina Hernandez Penna, DRA Global Labelling
BPI amendment 4	09-Mar-2010	02-Mar-2010	2010-PSB/GLC-0254-s	Amend CDS with the BPI/CDS with information to provide a 24 month update to the safety and efficacy data pertaining to the original indication: 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.	68-72	Robert A. Miranda, Senior Director, BU ONC Sandra Jullian, DRA Senior GL Manager

				Two-year extension data from two previous registration open label multicenter Phase II trials in patients with imatinib resistant or intolerant Ph+CML in accelerated phase and in patients with imatinib resistant or intolerant Ph+CML- in chronic phase (CAMN107A2101E1 and CAMN107A2101E2) is being used to support the safety and efficacy updates to the label.		
BPI amendment 5	31-Mar-2010	10-Dec-2009 24-Mar-2010	NA	Amend the BPI with information pertaining to the new proposed indication: treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukaemia (Ph+CML) in chronic phase. This amendment is based on data from one pivotal phase III randomized, openlabel, controlled, multicentre trial (CAMN107A2303) in patients with newly diagnosed Ph+CML in chronic phase is being used to support the safety and efficacy of the proposed indication. This trial compared two doses of Tasigna, 300 mg b.i.d. (new lower dose) and 400 mg b.i.d. (currently approved dose) to Glivec (imatinib) 400 mg q.d. (current standard of care).	73-80	Robert A. Miranda, Senior Director, BU ONC Sandra Jullian, DRA Senior GL Manager
BPI amendment 6	24-Nov-2010	09-Nov-2010	2010-PSB/GLC-0338-s	The reason for this amendment is a recent request from health authority for analysis of Tumor Lysis Syndrome (TLS) associated with Gleevec/Glivec (imatinib) use. This prompted the assessment of TLS associated with Tasigna (nilotinib) as both belong to the same class. In addition, TLS has been included in the US Package Insert (USPI) for Tasigna.	81	Robert A. Miranda, Senior Director, BU ONC Nicola B. Mertens, Tasigna Senior RBRM Sandra Jullian, DRA Senior GL Manager
BPI amendment 7	06-Dec-2010	23-Nov-2010	2010-PSB/GLC-0342-s	The reason for this amendment is to update the BPI with information regarding the recently completed 2-year carcinogenicity (CAR) study in rats. This amendment does not impact the Basic Patient Leaflet or the Basic Succinct Statement.	82-83	Robert A. Miranda, Senior Director, BU ONC Nicola B. Mertens, Tasigna Senior RBRM Sandra Jullian, DRA Senior GL Manager
BPI amendment 8	04-Feb-2011	21-Dec-2011	2010-PSB/GLC-0360-s	The principal reason for this amendment is to update the BPI with information pertaining to the indication: treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukaemia (Ph+CML) in chronic phase. This amendment is based on data from the 24 month update to the pivotal phase III randomized, open-label, controlled, multicentre trial (CAMN107A2303) in patients with newly diagnosed Ph+CML in chronic phase.	84-85	Robert A. Miranda, Senior Director, BU ONC Nicola B. Mertens, Tasigna Senior RBRM Sandra Jullian, DRA Senior GL Manager
BPI amendment 9	19-May-2011	26-Apr-2011	2011-PSB/GLC-0401-s	The reason for this amendment is to update the BPI/CDS with information	86	Robert A. Miranda, GPRD

				pertaining to Peripheral Arterial Occlusive Disease (PAOD). The Tasigna® (nilotinib) Periodic Safety Update Report (PSUR 6) identified peripheral arterial occlusive disease (PAOD) as a new safety signal. Whilst acknowledging that this signal required further characterization the PSUR recommended that the CDS, Investigator Brochure, and Informed Consent Form be updated with information on PAOD. Consistent with this recommendation, there was a systematic review of information from all sources including published literature, the Novartis safety database, epidemiological evaluation and pre-clinical studies has been performed (see "Clinical Overview–Peripheral Arterial Occlusive Disease").		Sandra Jullian, DRA Sr. GPRM
BPI amendment 10	02-Mar-2012	31-Jan-2012	2012-PSB/GLC-0527-s	The reason for this amendment is to update the BPI/CDS with the phase III study in newly diagnosed patients with Ph+ CML in chronic phase: The clinical and efficacy data has been updated to reflect when patients completed 36 months of treatment (or discontinued earlier), as well as to reflect the relative bioavailability of nilotinib: This study was undertaken as a post-marketing study commitment for the US FDA.. The Tasigna CDS/BPI labeling has been updated to include this data. In addition, this BPI amendment corrects an error in Section 5.3 Preclinical Safety Data pertaining to the exposure (in terms of AUC) reported for the carcinogenicity study.	87-90	Robert A. Miranda, GPRD Andras Megyeri, DRA GI-TAL Onc
BPI amendment 11	27-Jul-2012	21-Jun-2012	2012-PSB/GLC-0557-s	The principal reason for this amendment is to update the labeling with information pertaining to data from a recently completed drug interaction study to evaluate the effects of two gastric pH-elevating agents, famotidine and an antacid preparation, on the pharmacokinetics of nilotinib in healthy subjects. Based on data from this study a lack of significant drug-drug interaction can be claimed based on the observed PK findings and a labelling change is recommended (see supporting Clinical Overview). This study was undertaken as a post-marketing study commitment for the US FDA (final report submission date is June 2012).	91-92	Karen Habucky, GPRD Glivec/Tasigna Andras Megyeri, DRA GL-TAL Onc
BPI amendment 12	18-Apr-2013	20-Feb-2013	2012-PSB/GLC-0565-s	The amendments related to Sections 4.2, 4.4, 4.8 and 5.1 were initiated upon completion of the yearly analysis of the 48 months' data from ENESTnd (CAMN107A2303) clinical trial. In addition, the Novartis safety database Argus search and worldwide published literature search, were also reviewed.	93-98	Karen Habucky, GPRD Glivec/Tasigna Andras Megyeri, DRA GL-TAL Onc

1.0	31-Jul-2013	11-Jun-2013	2013-PSB/GLC-0627-s	Section Dosage and administration: – addition of glucose monitoring recommendation; Section Warning and precautions – addition of blood glucose laboratory monitoring recommendation; Section Interactions – addition of information on anticipated interaction with lipid lowering agents; Section WOCBP – recommendation was added for highly effective contraception for 2-weeks after ending treatment. Additionally there were editorial changes as the BPI format was converted to the CDS format. Please note that the subsection 4.7 of the BPI "Effects on ability to drive and use machines" was taken out as there are no specific reports related to the ability of driving and using machines. Dizziness and visual impairment ADRs does not warrant including in the CDS Warning and precaution section and it was removed as per Novartis CDS template and Business Guidance for completing Drug-Safety-related sections of the CDS.	99-102	Karen Habucky, GPRD Glivec/Tasigna Andras Megyeri, DRA GL-TAL Onc
1.1	17-Jan-2014	10-Dec-2013	2013-PSB/GLC-0670-s	Section 6 Warnings and precautions: -inclusion of a warning and monitoring recommendation for cardiovascular events Section 7 Adverse drug reactions: -inclusion of three additional adverse drug reaction terms (transient ischemic attack, intermittent claudication, and arterial stenosis limb) under the 'Additional Data from Clinical Trials' as cardiovascular events. Additionally there were some minor editorial changes throughout the CDS. The BPL and BSS were also amended based on the above CDS changes.	103	Karen Habucky, GPRD Glivec/Tasigna Andras Megyeri, DRA GL-TAL Onc
1.2	24-Apr-2014	25-Feb-2014	2014-PSB/GLC-0676-s	CDS - section 6 Warnings and precautions: Inclusion of a warning related to 'severe fluid retention' in line with the approved EU SmPC language. The current Tasigna CDS already contained ADRs in various sections for fluid retention including; pleural/ pericardial effusions, pulmonary edema etc. This new warning focuses and supports the timely identification of causations and appropriate treatment interventions of the severe fluid retention. CDS - section 8 Interactions: Subsection 'Drugs that may have their systemic concentration altered by nilotinib' was updated based on the completion of a drug-drug interaction study with chronic administration of nilotinib in combination with midazolam, a CYP3A4 substrate (Study AMN107A2128). This new information was also referenced in section 6	104-105	Karen Habucky, GPRD Glivec/Tasigna Andras Megyeri, DRA GL-TAL Onc

				Warning and precautions / Laboratory tests and monitoring.		
1.3	06-May-2014	11-Mar-2014	2014-PSB/GLC-0682-s	The update of safety and efficacy data based on the 60 months follow-up of the phase III study in newly diagnosed patients with Ph+ CML in chronic phase (ENESTnd A2303 study).	106-110	Karen Habucky, GPRD Glivec/Tasigna Bruno Duverger, DRA GLM
1.4	25-Jul-2014	15-Jul-2014	NA	CDS - Section 4 Dosage and administration – inclusion of a statement about regular monitoring of efficacy of the treatment in CML patients. BPL - Section 1 What Tasigna is and what is it used for – The sentence about monitoring recommendation is moved from section 3 "How long to take Tasigna" to the section 1 "Monitoring your Tasigna treatment".; Section 2 Before you take Tasigna - Two edits are corrected in the "Taking other medicines" sub-section. The amendments of the CDS and BPL do not affect the BSS (unchanged).	111	Karen Habucky, GPRD Glivec/Tasigna Bruno Duverger, DRA GLM
1.5	13-Apr-2015	10-Mar-2015	2014-PSB/GLC-0729-s	CDS - Section 13 – Non Clinical Study – inclusion of the results from the 26-week mouse carcinogenicity study The changes have been reflected in the BSS. The amendment of the CDS do not affect the BPL (unchanged).	112-113	Karen Habucky, GPRD Glivec/Tasigna Bruno Duverger, DRA GLM
1.6	23-Mar-2016	01-Mar-2016	2016-PSB/GLC-0808-s	The main reason for this amendment is to incorporate new safety information related to "hepatitis B reactivation". Following the assessment on hepatitis B reactivation for all BCR-ABL TKIs by the European Pharmacovigilance Risk Assessment Committee (PRAC) in which all available data on cases related to reactivation of hepatitis B virus (HBV) in patients treated with BCR-ABL TKIs have been reviewed, the PRAC concluded that there is convincing evidence of a class-effect among BCR-ABL TKIs compounds with documented cases of HBV reactivation.	114	Raluca Kreft, GPRD Glivec/Tasigna Victoria Kozlovsky, DRA GLM
1.7	15-Jul-2016	07-Jun-2016	2016-PSB/GLC-0824-s	The main reason for this amendment is to incorporate (TFR studies ENESTfreedom and ENESTop as well as clinical trial data from ENESTcmr.	115-118	Raluca Kreft, GPRD Glivec/Tasigna Victoria Kozlovsky, DRA GLM

				Safety Labelling Change was made to the following section of the CDS v1.7 and needs to be implemented by the CPOs (independent of the TFR submission). Addition of ADR describing an increase in musculoskeletal pain after Tasigna discontinuation Section 7 - Adverse drug reactions		
1.8	05-Dec-2016	11-Oct-2016	NA	The main reason for this amendment is to include the pediatric data, specifically the extension of the current nilotinib indication for the treatment of pediatric patients with newly diagnosed Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase (Ph+ CML-CP) or with Ph+ CML-CP resistant or intolerant to prior therapy including imatinib and to include the new Tasigna 50 mg capsule strength developed for dosing of pediatric patients with small body weight and children who cannot swallow the available 150 mg or 200 mg capsule.	119-123	Raluca Kreft, GPRD Glivec/Tasigna Victoria Kozlovsky, DRA GLM
2.0	30-Jan-2018	12-Dec-2017	2017-PSB/GLC-0916-s	Comprehensive review and update of the Tasigna CDS taking into account the associated labels from key regions and countries, and pharmacovigilance activities.	124	Raluca Kreft, GTAL Glivec/Tasigna Victoria Kozlovsky, DRA GLM
2.1	25-Mar-2019	29-Jan-2019	2018-PSB/GLC-0954-s	The main reason for this amendment is to incorporate new safety information related to “growth retardation” based on study CAMN107A2203, in sections 6 Warnings and Precautions, and 7 Adverse drug reactions.	125	Raluca Kreft, GTAL CML&Benign hematology Victoria Kozlovsky, DRA GLM
2.2	18-May-2020	20-Apr-2020	2020-PSB/GLC-1097-s	Amend - Facial paralysis		Kozlovsky V

List of abbreviations

ADR	Adverse drug reaction
AP	Accelerate phase
ALT	Alanine transaminase
AST	Aspartate aminotransferase
AUC	Area under the curve
b.i.d	twice daily
CCyR	Complete cytogenetic response
CDS	Core Data Sheet
CHR	Complete hematologic response
CIOMS	Council for International Organizations of Medical Sciences
CML	Chronic myeloid leukemia
CMR	Complete molecular response
CNS	Central nervous system
CP	Chronic phase
CSF1R	Colony stimulating factor 1 receptor
CSI	Core Safety Information
CTC	Common toxicity criteria
DDR	Discoidin domain receptor
ECG	Electrocardiogram
G-CSF	Granulocyte colony-stimulating factor
GL	Global Labeling
GLC	Global Labeling Committee
HMG-CoA	Hydroxymethylglutaryl-CoA
HR	Hematologic response
INN	International non-proprietary name
IS	International scale
MCyR	Major cytogenetic response
MR	Molecular response
MMR	Major molecular response
MOA	Mechanism of action
NCI	National Cancer Institute
NEL	No evidence of leukemia
NOEL	No-observed-effect-levels
NOAEL	No-observed-adverse-effect-levels
OS	Overall Survival
PD	Pharmacodynamics
PDGF	Platelet-derived growth factor
Ph+ CML	Philadelphia chromosome positive chronic myeloid leukemia
PK	Pharmacokinetics
RA	Regulatory Affairs
RQ-PCR	Real-time quantitative polymerase chain reaction

SLC(s)	Safety Label Change(s)
TFR	Treatment-free remission
TLS	Tumor lysis syndrome
TKI	Tyrosine kinase inhibitor
LVEF	Left ventricular ejection fraction