NOVARTIS

Tasigna® (nilotinib hydrochloride)

150 mg and 200 mg, capsule

Professional Information

Document status: Final

Release date: 30 June 2022

SCHEDULING STATUS **S4**

1. NAME OF THE MEDICINE

TASIGNA® 150 mg capsule

TASIGNA® 200 mg capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TASIGNA® 200 mg capsule:

Each capsule contains nilotinib hydrochloride monohydrate equivalent to 200 mg nilotinib base.

Contains sugar: 156,11 mg of lactose

TASIGNA® 150 mg capsule:

Each capsule contains nilotinib hydrochloride monohydrate equivalent to 150 mg nilotinib base.

Contains sugar: 117,08 mg of lactose

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

TASIGNA® 200 mg capsule: Whitish to yellowish powder in light yellow opaque hard gelatin capsules, size 0 with red axial imprint “NVR/TKI”.

TASIGNA® 150 mg capsule: Whitish to yellowish powder in red opaque hard gelatin capsules, size 1 with black axial imprint “NVR/BCR”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) in chronic phase. 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 4.4 and 5.1).

Treatment of chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) in adult patients resistant to or intolerant to at least one prior therapy including imatinib. 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 4.4 and 5.1).

The term “sustained deep molecular response”, is defined by the following criteria (see section 5.1 Pharmacodynamic properties: Clinical efficacy and safety).

For patients with newly diagnosed Ph+ CML - CP:

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

For Ph+ CML - CP patients with at least one prior therapy including imatinib:

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

4.2 Posology and method of administration

Therapy should be initiated by a medical practitioner experienced in the treatment of patients with CML.

Posology

Dosing in patients with newly diagnosed Ph+ CML - chronic phase:

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

Dosing in patients with Ph+ CML - chronic phase and CML - accelerated phase resistant to or intolerant to at least one prior therapy including imatinib:

The recommended dose of TASIGNA is 400 mg twice daily. Treatment should be continued as long as the patient continues to benefit.

Philadelphia chromosome positive CML patients in chronic phase who have been treated with TASIGNA as first-line therapy and who achieved a sustained deep molecular response (MR4.5):

Discontinuation of treatment may be considered in eligible Philadelphia chromosome positive (Ph+) CML patients in chronic phase 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 therapy

should be initiated by a medical practitioner experienced in the treatment of patients with CML (see sections 4.4 and 5.1).

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

For patients who lose MR4 (MR4 = BCR – ABL / ABL ≤ 0.01 % IS) but not MMR (MMR = BCR – ABL / ABL ≤ 0.1 % IS) during the treatment-free phase, BCR - ABL transcript levels should be monitored every 2 weeks until BCR - ABL levels return to a range between MR4 and MR4.5. Patients who maintain BCR - ABL levels between MMR and MR4 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 and every 12 weeks thereafter (see section 4.4).

Monitoring recommendations and dose adjustments or modifications:

Increases in total serum cholesterol levels have been reported with TASIGNA therapy (see section 4.4).

Lipid profiles should be determined prior to initiating TASIGNA therapy, assessed at month 3 and 6 after initiating therapy, and at least yearly during chronic therapy.

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

Due to possible occurrence of Tumor Lysis Syndrome (TLS) correction of clinically significant dehydration and treatment of high uric acid levels are recommended prior to initiating therapy with TASIGNA (see section 4.8), and medical practitioners should consider prescribing concomitant uric acid lowering medicines on an individual patient basis.

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

Table 1 Dose Adjustments for Neutropenia and Thrombocytopenia

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

400 mg twice daily		
• Resistant or intolerant CML in accelerated phase at 400 mg twice daily	(ANC) < 0,5 x 10^9 / L or platelet counts < 10 x 10^9 / L	1. Stop TASIGNA and monitor blood counts. 2. Resume within 2 weeks at prior dose if ANC > 1.0 x 10^9 / L and/or platelets > 20 x 10^9 / L. 3. If blood counts remain low, a dose reduction to 400 mg once daily may be required.

*ANC = absolute neutrophil count

If clinically significant moderate or severe non-haematologic toxicity develops, dosing should be interrupted, and may be resumed at 400 mg once daily once the toxicity has resolved. If clinically appropriate, re-escalation of the dose to 300 mg (newly diagnosed Ph+ CML - CP) or 400 mg (resistant or intolerant Ph+ CML - chronic phase and CML - accelerated phase) twice daily should be attempted.

Asymptomatic serum lipase elevations were observed and also elevations associated with clinical symptoms such abdominal pain or a diagnosis of pancreatitis. Elevations in serum lipase did not lead to treatment discontinuation in any patient in clinical studies.

Overall, this finding was clinically manageable in the majority of patients without requirement for dose reduction or interruption. For Grade 3 to 4 lipase elevations, doses were reduced to 400 mg once daily (see section 4.8).

In clinical studies, the majority of bilirubin and hepatic transaminase laboratory abnormalities in patients were of low-grade toxicity which did not require dose interruption or reduction.

Treatment discontinuation due to elevated serum bilirubin occurred in only 1 patient (0,3 %).

For Grade 3 to 4 bilirubin or hepatic transaminase elevations, doses were reduced to 400 mg once daily (see section 4.8).

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

Special populations

Elderly patients:

Approximately 12 % and 30 % of subjects in clinical studies (newly diagnosed Ph+ CML - CP and resistant or intolerant Ph+ CML - Chronic Phase and CML - Accelerated Phase) were 65 or over.

No major differences were observed for safety and efficacy in patients ≥ 65 years of age as compared to adults 18 to 65 years of age.

Patients with renal impairment:

Clinical studies have not been performed in patients with impaired renal function. Clinical studies 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. Total body clearance is not anticipated in patients with renal impairment

Patients with hepatic impairment:

TASIGNA has not been investigated in patients with hepatic impairment. Clinical studies have excluded patients with ALT and/or AST > 2,5 (or > 5, if related to disease) times the upper limit

of the normal range and/or total bilirubin > 1,5 times the upper limit of the normal range. Metabolism of nilotinib is mainly hepatic.

Cases of hepatic failure including fatal outcome have occurred in patients treated with TASIGNA (see section 4.8).

Cardiac disorders:

In clinical studies, patients were excluded with clinically significant cardiac syndromes (e.g. complete left bundle branch block, unstable angina, uncontrolled congestive heart failure, or recent myocardial infarction).

Paediatric population

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

TASIGNA should not be used in these categories of patients.

Method of administration

TASIGNA should be taken twice daily approximately 12 hours apart and should not be taken with food. The capsules should be swallowed whole with water. No food should be consumed for at least 2 hours before the dose is taken and no additional food should be consumed for at least one hour after the dose is taken (see section 4.4, 4.5 and 5.2).

For patients who are unable to swallow capsules, the content of each capsule may be dispersed in one teaspoon of applesauce (pureed apple) and be taken immediately.

Not more than one teaspoon of applesauce and no food other than applesauce must be used. (See section 4.5 and 5.2).

4.3 Contraindications

Known hypersensitivity to nilotinib or to any of the excipients. Safety in pregnancy and lactation has not been established “(see section 4.6)”

4.4 Special warnings and precautions for use

QT prolongation:

TASIGNA prolongs the QT interval. Correct hypokalaemia or hypomagnesaemia prior to administration and monitor periodically. Avoid concomitant therapy with medicines known to prolong the QT interval and strong CYP3A4 inhibitors. Use caution in patients with hepatic impairment. Obtain ECGs at baseline, seven days after initiation, and periodically thereafter, as well as following any dose adjustments.

TASIGNA should be used with caution in patients who have or may develop prolongation of QTc. These include patients with hypokalaemia or hypomagnesaemia, patients with congenital long QT syndrome, patients taking anti-dysrhythmic medicines or other medicines that may lead to QT prolongation, and cumulative high-dose anthracycline therapy.

Hypokalaemia or hypomagnesaemia must be corrected prior to TASIGNA administration.

Sudden deaths:

There were sudden deaths reported in the safety population and the expanded access program, post-marketing and the expanded access program and post-marketing. Ventricular repolarisation abnormalities may have contributed to their occurrence.

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, cardiovascular events included occurred in 7,5 % of patients at 300 mg and 13,4 % at 400 mg twice a day in particular ischaemic heart disease events occurred in 3,9 % and 8,7 % respectively; peripheral arterial occlusive disease resulted occurred in 2,5 % of patients at both 300 mg and 400 mg twice a day and resulted in withdrawal in 0,4 % and 1,1 % of patients at 300 mg and 400 mg twice a day, respectively.

TASIGNA should not be used as first line therapy in patients with prior severe peripheral arterial occlusive disease (PAOD), including angina pectoris. In patients with mild to moderate pre-existing PAOD, nilotinib may be prescribed with caution. 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 prior to initiating and during TASIGNA therapy according to standard guidelines (please refer to section 4.2).

Fluid retention:

Severe fluid retention manifestations occurred in 8 % of patients treated with TASIGNA. These cases included patients developing pleural effusion, peri-cardial effusion, including cardiac tamponade (0.1 – 1 %). Unexpected, rapid weight gain should be carefully investigated.

If signs of severe fluid retention appear during treatment with TASIGNA, the aetiology should be evaluated and patients treated accordingly (please refer to dosage and directions for use and side effects).

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 TASIGNA. Some cases involving medicines of the BCR - ABL TKI class resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or death.

Patients should be tested for hepatitis B infection before initiating treatment with TASIGNA. Patients currently on TASIGNA 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 TASIGNA should be frequently monitored for signs and symptoms of active hepatitis B infection throughout therapy and for several months following termination of therapy.

Special monitoring of Ph+ CML patients in chronic phase who have achieved a sustained deep molecular response.

Eligibility for discontinuation of treatment:

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

Monitoring of patients who have discontinued therapy:

Frequent 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 / ABL ≤ 0.0032 % IS). BCR - ABL transcript levels must be assessed prior to and during treatment discontinuation (see sections 4.2 and 5.1).

Loss of major molecular response (MMR = BCR – ABL / ABL ≤ 0.1 % IS) or confirmed loss of MR4 (two consecutive measures separated by at least 4 weeks showing loss of MR4 (MR4 = BCR – ABL / ABL ≤ 0.01 % IS)) will trigger treatment re-initiation within 4 weeks of when loss of remission is known to have occurred. Molecular relapse can occur during the treatment-free phase, and long-term outcome data are not yet available. It is therefore crucial to perform frequent monitoring of BCR - ABL transcript levels and complete blood count with differential in order to detect possible loss of remission (see section 4.2). For patients who fail to achieve MMR after three months of treatment re initiation, BCR - ABL kinase domain mutation testing should be performed.

Myelosuppression:

Treatment with TASIGNA is associated with thrombocytopenia, neutropenia and anaemia (NCI CTC Grade 3 / 4). The occurrence is more frequent in patients with imatinib-resistant or intolerant CML and, in particular in patients with Chronic Myelogenous Leukaemia-Accelerated Phase (CML-AP).

Complete blood counts should be performed every two weeks for the first 2 months and then monthly thereafter, or as clinically indicated. Myelosuppression was generally reversible and usually managed by withholding TASIGNA temporarily or reducing the dose (see section 4.2).

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.

Liver function abnormality:

TASIGNA may result in elevations in bilirubin, AST / ALT, and alkaline phosphatase. Check hepatic function tests periodically.

Electrolyte abnormalities:

TASIGNA can cause hypophosphataemia, hypokalaemia, hyperkalaemia, hypocalcaemia, and hyponatraemia. Correct electrolyte abnormalities prior to initiating TASIGNA and monitor periodically during therapy.

Hepatic impairment:

TASIGNA has not been investigated in patients with hepatic impairment. Clinical studies have excluded patients with ALT and or AST > 2,5 (or > 5, if related to disease) times the upper limit of 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 section 4.2).

Caution is recommended in these patients and QT interval should be monitored closely.

Interactions:

Avoid concomitant use of strong inhibitors or inducers of CYP3A4. If patients must be co-administered a strong CYP3A4 inhibitor, dose reduction should be considered and the QT interval should be monitored closely.

Total gastrectomy:

The bioavailability of nilotinib may be reduced in patients with total gastrectomy. More frequent follow up of these patients should considered.

Tumour lysis syndrome:

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

Food effect:

The bioavailability of TASIGNA is increased by food. TASIGNA should not be taken in conjunction with food (see section 4.2 and 4.6) and should be taken 2 hours after a meal. No food should be consumed for at least one hour after the dose is taken.

For patients who are unable to swallow capsules, the content of each capsule may be dispersed in one teaspoon of applesauce (pureed apple) and should be taken immediately.

Not more than one teaspoon of applesauce and no food other than applesauce must be used.

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

Class effects:

Class effects of Tyrosine Kinase Inhibitors (TKIs) such as contained in TASIGNA.

Although TKIs may have different kinase inhibition profiles and/or off target binding profiles, there is some evidence that the TKIs share to a variable degree, class related cerebrovascular adverse events (e.g. cerebrovascular accident, transient ischaemic attack, ischaemic stroke, and cerebral infarction).

These cerebrovascular adverse events may occur in patients on treatment with TKIs with or without risk factors for these events and may occur at any time during treatment with TKIs.

Patients on treatment with TASIGNA should be carefully monitored, and relevant risk factors managed to reduce the risk for these class related cerebrovascular adverse events.

Treatment with TASIGNA should be discontinued, and alternative treatment options be considered in patients who developed these class related cerebrovascular adverse events.

Laboratory tests and monitoring:

Blood lipids

In a Phase III study in newly diagnosed CML patients 27,6 % on 300 mg TASIGNA twice daily and 26,7 % on 400 mg TASIGNA twice daily developed total cholesterol abnormalities or had worsening of total cholesterol abnormalities and 1,1 % had grade 3 / 4 elevations in serum cholesterol. 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 once yearly during chronic therapy (see section 4.2). If a HMG CoA reductase inhibitor, (a lipid lowering agents) is needed, please refer to Interactions (Interaction with other medicinal products and other forms of interaction) before starting treatment since certain HMG CoA reductase inhibitors are also metabolised by the CYP3A4 pathway.

Blood glucose

In a Phase III study in newly diagnosed CML patients, 6,9 % of the patients treated with 400 mg nilotinib twice a day had a Grade ¾ 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 (please refer to section 4.2). If test results warrant therapy, physicians should follow their local standards of practice and treatment guidelines.

Lactose

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

4.5 Interaction with other medicines and other forms of interaction

Medicines that inhibit or Induce cytochrome P450 3A4 enzymes:

Nilotinib undergoes metabolism by CYP3A4, and concomitant administration of strong inhibitors or inducers of CYP3A4 can increase or decrease nilotinib concentrations significantly.

Ketoconazole: In healthy subjects receiving ketoconazole, a CYP3A4 inhibitor, at 400 mg once daily for 6 days, systemic exposure (AUC) to nilotinib was increased approximately 3-fold. (See section 4.4).

Similar changes are possible with other azole antifungal medicines such as itraconazole.

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

Medicines that may increase nilotinib serum concentrations:

Nilotinib is mainly metabolised in the liver, with CYP3A4 expected to be the main contributor to the oxidative metabolism. Nilotinib is also a substrate for the multi-medicine efflux pump, P-glycoprotein (Pgp). Therefore, absorption and subsequent elimination of systemically absorbed nilotinib may be influenced by medicines that affect CYP3A4 and/or Pgp. The bioavailability of nilotinib in healthy subjects was increased by 3-fold when co administered with the strong CYP3A4 inhibitor ketoconazole. Concurrent treatment with strong CYP3A4 inhibitors should therefore be avoided. (including but not limited to ketoconazole, itraconazole, voriconazole, ritonavir, clarithromycin and telithromycin) (see section 4.2 and 4.4 regarding QT prolongation).

Alternative concomitant medications with no or minimal CYP3A4 inhibition should be considered.

Antidysrhythmic medicines and other medicines that may prolong QT:

TASIGNA should be used with caution in patients who have or may develop prolongation of QT including those patients taking anti-dysrhythmic medicines such as amiodarone, disopyramide, procainamide, quinidine and sotalol or other medicines that may lead to QT disopyramide, procainamide, quinidine and sotalol or other medicines that may lead to QT

prolongation such as chloroquine, halofantrine, clarithromycin, haloperidol and methadone. (See section 4.4)

Medicines that may decrease nilotinib serum concentrations:

Inducers of CYP3A4 activity could increase the metabolism of nilotinib and thereby decrease plasma concentrations of nilotinib.

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

Nilotinib has pH-dependent solubility, with lower solubility at higher pH. In healthy subjects receiving esomeprazole at 40 mg once daily for 5 days, gastric pH was markedly increased, but nilotinib absorption was only decreased modestly (27 % decrease in C_{max} and 34 % decrease in AUC0 - ∞). TASIGNA may be used concurrently with esomeprazole or other proton pump inhibitors as needed.

In a healthy subjects study, no significant change in nilotinib pharmacokinetics was observed when a single 400 mg dose of TASIGNA was administered 10 hours after and 2 hours before famotidine. Therefore, when the concurrent use of a H_2 blocker is necessary, it may be administered approximately 10 hours before and approximately 2 hours after the dose of TASIGNA.

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

Medicines that may have their systemic concentration altered by nilotinib:

Nilotinib is identified as a competitive inhibitor of CYP3A4, CYP2C8, CYP2C9, and CYP2D6 in vitro, with Ki value being lowest for CYP2C9 (Ki = 0,13 microM). Enzyme induction studies indicate that nilotinib can be considered to be an *in vitro* inducer of CYP2B6, CYP2C8 and CYP2C9 activities.

In CML patients, TASIGNA 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 medicines primarily metabolised by CYP3A4 (e.g. certain HMG - CoA reductase inhibitors) may be increased when co-administered with TASIGNA. Appropriate monitoring and dose adjustment may be necessary for medicines that are CYP3A4 substrates and have a narrow therapeutic index (including but not limited to alfentanil, ciclosporin, dihydroergotamine, ergotamine, fentanyl, sirolimus and tacrolimus) when co-administered with TASIGNA.

In healthy subjects, TASIGNA 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.

Concomitant treatment with cholesterol lowering agents (e.g. statins), which are metabolised via the CYP3A4 pathway, should be administered with caution since systemic exposure may increase (see section 4.4).

Other interactions that may affect serum concentrations:

The absorption of TASIGNA is increased if it is taken with food, resulting in higher serum concentration (see section 4.2, 4.4 and 5.2).

TASIGNA should not be taken in conjunction with food and should be taken at least 2 hours after a meal. No food should be consumed for at least one hour after the dose is taken.

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

4.6 Fertility, pregnancy and lactation

TASIGNA should not be used during pregnancy as safety and efficacy in pregnancy and lactation has not been established.

Fertility:

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

Sexually active males taking TASIGNA should also use highly effective contraception TASIGNA remains in semen for up to 2 weeks after ending treatment.

Pregnancy:

TASIGNA can cause fetal harm when administered to a pregnant woman.

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.

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

Breastfeeding:

Studies in animals demonstrate that nilotinib is excreted into breast milk.

The effects of low-dose exposure of the infant to nilotinib are unknown, Because of the potential for serious adverse reactions in the breastfed child, breastfeeding is contraindicated during treatment and for at least 15 days after stopping treatment with TASIGNA.

4.7 Effects on ability to drive and use machines

Patients experiencing dizziness, visual impairment or other undesirable effects with a potential impact on the ability to safely drive or use machines should refrain from these activities as long as these undesirable effects persist. (See section 4.8).

4.8 Undesirable effects

In patients with newly diagnosed Ph+ CML - chronic phase:

The data reported below reflect exposure to TASIGNA from a randomised phase III study in patient with newly diagnosed Ph+ CML in chronic phase treated at the recommended dose of

300 mg twice daily (n = 279). The median time on treatment was 60,5 months (range 0,1 – 70,8 months).

Non-haematologic adverse drug reactions (ADR's) reported with very common frequency (≥ 10 %) were rash, pruritus, headache, nausea, fatigue, alopecia and myalgia, and upper abdominal pain. Most of these ADRs were mild to moderate in severity (Grade 1 or 2).

Constipation, diarrhoea, dry skin, muscle spasms, arthralgia, abdominal pain, peripheral oedema, vomiting and asthenia were observed commonly (in 5 – 10 %) and have been of mild to moderate severity, manageable and generally did not require dose reduction. Pleural and pericardial effusions, regardless of causality occurred in 2 % and < 1 % of patients, respectively, receiving TASIGNA 300 mg twice daily. Gastrointestinal haemorrhage, regardless of causality was reported in 3 % of these patients. The change from baseline in mean time - averaged QTcF interval steady state in the nilotinib recommended dose of 300 mg twice daily was 6 msec. In the nilotinib 400 mg twice daily group the mean time - averaged QTcF increase at steady state were 6 msec. No patient had an absolute QTcF of > 500 msec while on study medicine in any of the treatment groups and no events of Torsade de Pointes were observed. QTcF increases from baseline that exceed 60 msec were observed in 4 patients while on study medicine (one in the 300 mg twice daily treatment group and four in the 400 mg twice daily treatment group).

No patients in any treatment groups had a LVEF < 45 % during treatment. Also, there were no patients with 15 % or greater decrease from baseline in LVEF. No sudden deaths have been reported.

In the nilotinib 300 mg twice daily group, haematologic ADR's include myelosuppression: thrombocytopenia (18 %), neutropenia (15 %), and anaemia (8 %). Biochemistry ADRs include alanine aminotransferase increased (24 %), hyperbilirubinaemia (16 %), aspartate aminotransferase increased (12 %), lipase increased (11 %), blood bilirubin increased (10 %),

hyperglycaemia (4 %), hypercholesterolaemia (3 %), and hypertriglyceridaemia (< 1 %) See Table 3 for grade 3 / 4 laboratory abnormalities.

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

ADRs in patients with resistant or intolerant Ph+ CML - chronic phase (CP) and CML - Accelerated phase (AP):

The data reported below reflect exposure to TASIGNA in 458 patients with Ph+ Chronic myelogenous Leukaemia - chronic phase (CML - CP) (n = 321) and chronic myelogenous leukaemia-accelerated phase (CML - AP) (n = 137) resistant to or intolerant to at least one prior therapy including imatinib in an open-label multicentre study treated at the recommended dose of 400 mg twice daily.

Non-haematologic adverse drug reactions (ADR's) reported with very common frequency (≥ 10 % in the combined chronic myelogenous leukaemia chronic phase (CML - CP) and chronic myelogenous leukaemia – accelerated phase (CML - AP) patient populations) were rash, pruritus, nausea, fatigue, headache, constipation, diarrhoea vomiting and myalgia.

Most of these ADR's were mild to moderate in severity. Vomiting, myalgia, alopecia, muscle spasms, decreased appetite, arthralgia, bone pain, abdominal pain, peripheral oedema and asthenia were observed in 5 % to 10 % and have been of mild to moderate severity (Grade 1 or 2).

Discontinuation for adverse events regardless of causality was observed in 16 % of CP and 10 % of AP patients.

Pleural and pericardial effusions as well as complications of fluid retention occurred in 1 % of patients receiving TASIGNA. Congestive heart failure was observed in 1 % of patients.

Gastrointestinal and CNS haemorrhage were reported in 3 % and 1 % of patients, respectively. Sudden deaths and QT prolongation were reported. QTcF exceeding 500 msec respectively. Sudden deaths and QT prolongation were reported. QTcF exceeding 500 msec was observed in < 1 % of patients.

Haematologic ADR's include myelosuppression: thrombocytopenia (31 %), neutropenia (17 %), and anaemia (14 %). See Table 3 for grade 3 / 4 laboratory abnormalities.

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

Table 2 shows the percentage of patients experiencing treatment-emergent adverse reactions (excluding laboratory abnormalities) regardless of relationship to study medicine. Adverse reactions reported in at least 10 % of patients who received at least one dose of TASIGNA are listed.

Table 2: Treatment-Emergent Adverse Reactions reported in > 10 % of Patients in the Clinical Study[a]

		CML - CP N = 318		**CML - AP N = 120**	
Body System and Preferred Term		**All Grades (%)**	**CTC Grades[b] 3 / 4 (%)**	**All Grades (%)**	**CTC Grades[b] 3 / 4 (%)**
Skin and subcutaneous tissue disorders	Rash	33	2	28	0
	Pruritus	29	1	20	0

Gastrointestinal disorders	Nausea	31	1	18	< 1
	Diarrhoea	22	3	19	2
	Constipation	21	< 1	18	0
	Vomiting	21	< 1	10	0
	Abdominal pain	11	1	13	3
Nervous system disorders	Headache	31	3	21	2
General disorders and administration site conditions	Fatigue	28	1	16	< 1
	Pyrexia	14	1	24	2
	Asthenia	14	0	12	2
	Oedema, peripheral	11	0	11	0
Musculoskeletal and connective tissue disorders	Arthralgia	18	2	16	0
	Myalgia	14	2	14	< 1
	Pain in extremity	13	1	16	2
	Bone pain	11	< 1	13	< 1
	Muscle spasms	11	< 1	14	0
	Back pain	10	< 1	12	< 1

Respiratory, thoracic and mediastinal disorders	Cough	17	< 1	13	0
	Dyspnoea	11	1	8	3
Infections and infestations	Nasopharyngitis	16	< 1	11	0

[a] Excluding laboratory abnormalities

[b] NCI Common Terminology Criteria for Adverse Events, Version 3.0

Table 3 shows the percentage of patients experiencing treatment-emergent Grade 3 / 4 laboratory abnormalities in patients who received at least one dose of TASIGNA.

Table 3: Incidence of Clinically Relevant Grade 3 / 4 Laboratory Abnormalities

	Newly diagnosed Ph+ CML - CP		**Resistant or intolerant Ph+**	
	TASIGNA 300 mg bd N = 279	**TASIGNA 400 mg bd N = 277**	**TASIGNA 400 mg bd CML - CP N = 321**	**TASIGNA 400 mg bd CML - AP N = 137**
Haematologic Parameters				
Myelosuppression				
Thrombocytopenia	10 %[1]	12 %[1]	30 %[1]	42 %[2]
Neutropenia[2]	12 %	10 %	31 %	42 %[3]
Anaemia	4 %	4 %	11 %	27 %
Biochemistry Parameters				
	9 %	10 %	18 %	18 %
Elevated lipase	7 %	10 %	17 %	15 %
Hypophosphataemia	4%	9 %	7 %	9 %
Elevated bilirubin (total)	4 %	9 %	4 %	4 %
Elevated ALT	1 %	3 %	3 %	2 %
Elevated AST	0 %	0 %	1 %	< 1 %
Elevated creatinine	0 %	1 %	**	**
Elevated Cholesterol (total)	0 %	< 1 %	**	**
Elevated triglycerides				

* NCI Common Terminology Criteria for Adverse Events, version 3.0

***Parameter not collected*

[1] CML - CP: Thrombocytopenia: 11 % were grade 3, 17 % were grade 4

[2] CML - AP: Thrombocytopenia: 7 % were grade 3, 30 % were grade 4

[3] CML - AP: Neutropenia: 12 % were grade 3, 25 % were grade 4

Treatment discontinuation in Ph+ CML patients in chronic phase who have achieved a sustained deep molecular response.

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

In a Phase II clinical study with newly diagnosed patients with Ph+ CML in chronic phase (N = 190), musculoskeletal symptoms were reported within a year of TASIGNA discontinuation in 24.7 % versus 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.

Additional data from clinical trials:

The following adverse reactions were reported in patients in the TASIGNA clinical studies at the recommended doses at a frequency of ≥ 5 %. The corresponding frequency category using the following convention (CIOMS III) is provided for each adverse reaction: (common is ≥ 1 /

100 and < 1 / 10; uncommon is ≥ 1 / 1,000 and < 1 / 100; single events are captured as unknown in frequency). For laboratory abnormalities, very common events (> 1 / 10) not included in Table 3 are also reported. These adverse reactions are included based on clinical relevance and are listed according to MedDRA system organ class.

The adverse reactions are ranked in decreasing order of frequency within each category, obtained from two clinical studies:

1. Newly diagnosed Ph+ CML - CP 60 months' analysis and 2. Resistant or intolerant studies:

1. Newly diagnosed Ph+ CML - CP 48 months' analysis and 2. Resistant or intolerant Ph+ CML - CP and CML - AP 24 months' analysis.

Infections and infestations:

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

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

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

Neoplasms Benign, Malignant and Unspecified:

Common: skin papilloma

Unknown frequency: oral papilloma, paraproteinaemia

Blood and lymphatic system disorders:

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

Unknown frequency: thrombocythaemia, leucocytosis

Immune system disorders:

Unknown frequency: hypersensitivity.

Endocrine disorders:

Uncommon: hyperthyroidism, hypothyroidism.

Unknown frequency: thyroiditis, secondary hyperparathyroidism

Metabolism and nutrition disorders:

Very common: hypophosphataemia

Common: electrolyte imbalance (including hypomagnesaemia, hyperkalaemia, hypokalaemia, hyponatraemia, hypocalcaemia, hypophosphataemia, hypercalcaemia), diabetes mellitus, hyperglycaemia, hypercholesterolaemia, hyperlipidaemia, hypertriglyceridemia, decreased appetite.

Uncommon: gout, dehydration, increased appetite, dyslipidaemia

Unknown frequency: hyperuricaemia, hypoglycaemia.

Psychiatric disorders:

Common: depression, insomnia, anxiety.

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

Nervous system disorders:

Common: dizziness, peripheral neuropathy, paraesthesia, hypoaesthesia.

Uncommon: intracranial haemorrhage, ischaemic stroke, transient ischaemic attack, cerebral infarction loss of consciousness (including syncope), migraine, tremor, disturbance in attention, hyperaesthesia.

Unknown frequency: 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.

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

Unknown frequency: papilloedema, diplopia, eye swelling, photophobia, blepharitis, eye pain, chorioretinopathy, allergic conjunctivitis.

Ear and labyrinth disorders:

Common: vertigo.

Unknown frequency: hearing impaired, ear pain, tinnitus.

Cardiac disorders:

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

Uncommon: cardiac failure, myocardial infarction, coronary artery disease and angina pectoris, cardiac murmur, pericardial effusion and tamponade, cyanosis.

Unknown frequency: pericarditis, ventricular dysfunction, ejection fraction decrease.

Vascular disorders:

Common: flushing, hypertension.

Uncommon: hypertensive crisis, peripheral arterial occlusive disease, haematoma, atherosclerosis, intermittent claudication, arterial stenosis limb.

Unknown frequency: shock haemorrhagic, hypotension, thrombosis, peripheral artery stenosis.

Respiratory, thoracic and mediastinal disorders:

Common: dyspnoea, exertional dyspnoea, epistaxis, cough, dysphonia.

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

Unknown frequency: pulmonary hypertension, wheezing, oropharyngeal pain.

Gastrointestinal disorders:

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

Uncommon: gastrointestinal haemorrhage, gastroesophageal reflux, melaena, mouth ulceration, stomatitis, dry mouth, gastritis, oesophageal pain, dysgeusia.

Unknown frequency: gastric ulcer, gastrointestinal ulcer perforation, retroperitoneal haemorrhage, haematemesis, ulcerative oesophagitis, sub-ileus, enterocolitis, haemorrhoids, hiatus hernia, rectal haemorrhage, sensitivity of teeth, gingivitis.

Hepatobiliary disorders:

Very common: Hyperbilirubinaemia

Common: abnormal hepatic function.

Uncommon: hepatotoxicity, hepatitis, jaundice.

Unknown frequency: cholestasis, hepatomegaly.

Skin and subcutaneous tissue disorders:

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

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

Unknown frequency: 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, flank pain, muscular weakness.

Uncommon: musculoskeletal stiffness, joint swelling.

Unknown frequency: arthritis.

Renal and urinary disorders:

Common: pollakiuria.

Uncommon: dysuria, micturition urgency, nocturia.

Unknown frequency: renal failure, haematuria, urinary incontinence, chromaturia.

Reproductive system and breast disorders:

Uncommon: breast pain, erectile dysfunction, gynaecomastia.

Unknown frequency: breast induration, menorrhagia, nipple swelling.

General disorders and administration site conditions:

Common: chest pain (including non-cardiac chest pain), pain (including neck pain and back pain), pyrexia, chest discomfort, malaise.

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

Unknown frequency: localised oedema.

Investigations:

Very common: increased alanine aminotransferase, increased aspartate aminotransferase, increased lipase, increased cholesterol (including low density and high-density lipoproteins), increased total cholesterol, increased blood triglycerides.

Common: decreased haemoglobin, increased blood amylase, decreased weight, increased gamma-glutamyltransferase, increased weight, increased blood creatinine phosphokinase, decreased globulins. increased blood alkaline phosphatase, increased blood insulin.

Uncommon: increased blood lactate dehydrogenase, increased blood urea.

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

Post-marketing Experience

The following adverse reactions have been derived from spontaneous case reports, literature cases, expanded access programs, and clinical studies other than the global registration trials. Because these reactions are reported from a population of uncertain size, it is not possible to estimate their frequency or establish a causal relationship to nilotinib exposure. Cases of tumour lysis syndrome and facial paralysis have been reported in patients treated with TASIGNA.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Isolated reports on intentional overdose with nilotinib were reported, where 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. In the event of overdose, the patient should be observed and appropriate supportive treatment given.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties:

Pharmacotherapeutic group: BCR - ABL tyrosine kinase inhibitors, ATC code: L01EA03.

Mechanism of action

Nilotinib is a potent and selective inhibitor of the ABL tyrosine kinase activity of the BCR - ABL oncoprotein both in cell lines and in primary Philadelphia-chromosome positive leukaemia cells.

Nilotinib binds with high affinity to 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 forms of BCR - $ABL_{[PM1]}$. As a consequence of this biochemical activity, nilotinib selectively inhibits the proliferation and induces apoptosis in cell lines and in primary Philadelphia-chromosome positive leukaemia cells from CML patients.

Clinical efficacy and safety

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

In an open-label, single-arm study, 215 adult patients with Ph+ CML in chronic phase treated with nilotinib in first - line for ≥ 2 years who achieved MR4.5 as measured with the MolecularMD MRDx™ BCR - ABL test were enrolled to continue nilotinib treatment for additional 52 weeks (nilotinib consolidation phase). 190 of 215 patients (88.4 %) entered the Treatment-free Remission (TFR) phase after achieving a sustained deep molecular response during the consolidation phase, defined by the following criteria:

- the 4 last quarterly assessments (taken every 12 weeks) were at least MR4 (BCR - ABL/ABL ≤ 0.01 % IS), and maintained for one year
- the last assessment being MR4.5 (BCR – ABL / ABL ≤ 0.0032 % IS)

- no more than two assessments falling between MR4 and MR4.5 (0.0032 % IS < BCR – ABL / ABL ≤ 0.01 % IS).

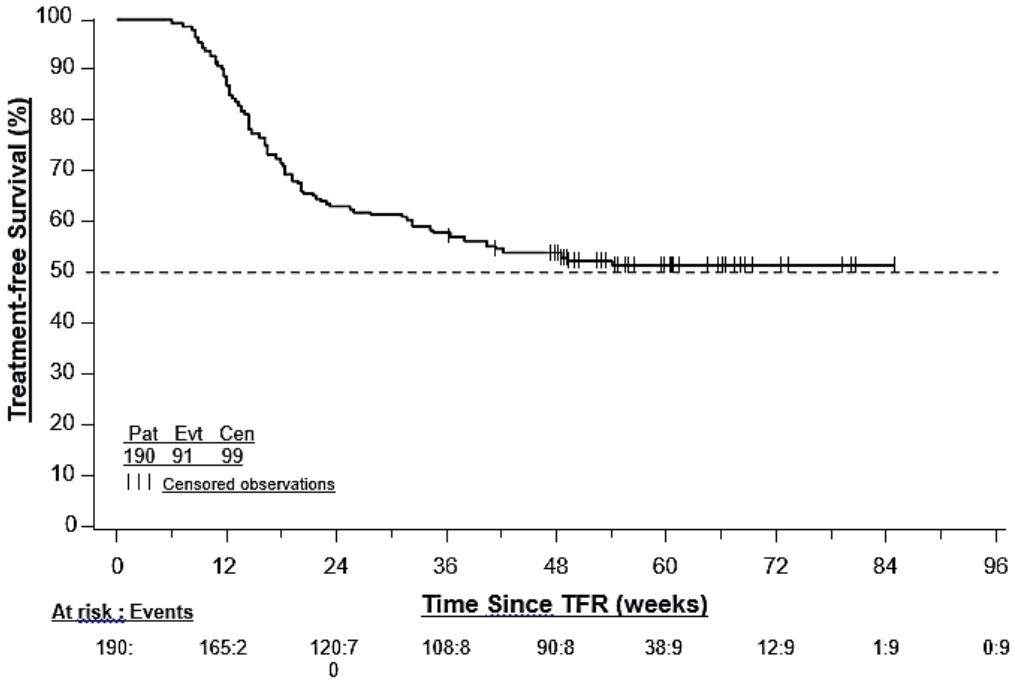
The primary endpoint was the percentage of patients in MMR at 48 weeks after starting the TFR phase (considering any patient who required re-initiation of treatment as non-responder). Of the 190 patients who entered the TFR phase, 98 patients (51.6 % [95 % CI: 44.2, 58.9]) were in MMR at 48 weeks.

Eighty - eight patients (46.3 %) discontinued 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 these 88 patients, 86 patients restarted nilotinib treatment and 2 patients permanently discontinued the study. Eighty-five of these 86 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 nilotinib treatment 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 and MR4.5 rates at 24 weeks of re-initiation were 98.8 % (95 % CI: 94.2, 99.9) and 90.9% (95 % CI: 83.2, 96.0), respectively.

The KM estimate of median treatment-free survival (TFS) has not yet been reached (Figure 1); 99 of 190 patients (52.1 %) did not have a TFS event.

Figure 1 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

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

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

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

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

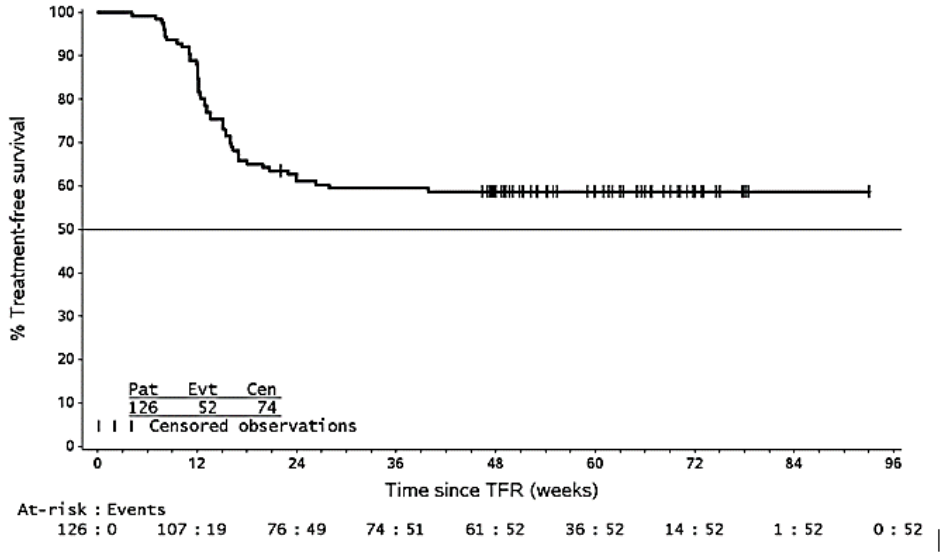
The primary endpoint was defined as the proportion of patients without confirmed loss of MR4.0 or loss of MMR within 48 weeks following discontinuation of TASIGNA therapy. Of the 126 patients who entered the TFR phase, 73 patients (57.9 %, [95 % CI: 48.8, 66.7]) had no loss of MMR, no confirmed loss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

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

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 2)

Figure 2 **Kaplan-Meier estimate of treatment-free survival after start of TFR (Full Analysis Set)**



5.2 Pharmacokinetic properties:

Absorption:

Peak concentrations of nilotinib are reached 3 hours after oral administration. Nilotinib absorption following oral administration was approximately 30 %. In healthy volunteers, C_{max} and area under the serum concentration-time curve (AUC) of nilotinib are increased by 112 % and 82 %, respectively compared to fasting conditions, when nilotinib is given with food.

Administration of nilotinib 30 minutes or 2 hours after food increased bioavailability of nilotinib by 29 % or 15 %, respectively (see section 4.2, 4.4 and 4.5).

Nilotinib absorption (relative bioavailability) may be reduced by approximately 48 % and 22 % in patients with total gastrectomy and partial gastrectomy, respectively.

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

Distribution:

Blood-to-plasma ratio of nilotinib is 0,68. Plasma protein binding is approximately 98 % on the basis of in vitro experiments.

Biotransformation:

Main metabolic pathways identified in healthy subjects are oxidation and hydroxylation. Nilotinib is the main circulating component in the serum.

None of the metabolites contribute significantly to the pharmacological activity of nilotinib.

Nilotinib is primarily metabolised by CYP3A4, with possible minor contribution from CYP2C8.[PM2]

Elimination:

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

Linearity / non-linearity:

Steady-state nilotinib exposure was dose-dependent with less than dose-proportional increases in systemic exposure at dose levels higher than 400 mg given as once daily dosing. Daily serum exposure to nilotinib of 400 mg twice - daily dosing at steady state was 35 % higher than with 800 mg once-daily dosing. Systemic exposure (AUC) of nilotinib at steady state at a dose level of 400 mg twice daily was approximately 13,4 % higher than with 300 mg twice daily.

The average nilotinib trough and peak concentrations over 12 months were approximately 15,7 % and 14,8 % higher following 400 mg twice daily dosing compared to 300 mg twice daily. There was no relevant increase in exposure to nilotinib when the dose was increased from 400 mg twice daily to 600 mg twice daily.

Characteristics in patients:

Steady state conditions were essentially achieved by day 8. An increase in serum exposure to nilotinib between the first dose and steady state was approximately 2-fold for daily dosing and 3,8-fold for twice-daily dosing. The apparent elimination half-life estimated from the multiple dose PK with daily dosing was approximately 17 hours. Inter-patient variability in nilotinib PK was moderate to high.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

TASIGNA® 200 mg capsule:

Capsule content:

Lactose monohydrate;

Crospovidone;

Poloxamer 188;

Colloidal silicon dioxide;

Magnesium stearate

Capsule shell:

Gelatin;

Titanium dioxide

Iron oxide, yellow

Printing ink:

Iron oxide, red

TASIGNA 150 mg capsule:

Capsule content:

Lactose monohydrate;

Crospovidone;

Poloxamer 188;

Colloidal silicon dioxide;

Magnesium stearate

Capsule shell:

Gelatin;

Titanium dioxide;

Iron oxide, yellow

Iron oxide, red

Printing ink:

Iron oxide, black

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 30 °C in the original package. Protect from moisture.

6.5 Nature and contents of container

TASIGNA® 200 mg capsule: 28 or 112 capsules in colourless, transparent PVC/PVDC (polyvinylchloride/polyvinylidene chloride) blisters with an aluminium foil backing.

TASIGNA® 150 mg capsule: 28 or 112 capsules in colourless, transparent PVC/PVDC (polyvinylchloride/polyvinylidene chloride) blisters with an aluminium foil backing.

Not all pack sizes may be marketed.

The blister foil is imprinted with the proprietary name, company name, batch number and expiry date. The blisters are packed into cardboard cartons.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

NOVARTIS SOUTH AFRICA (PTY) LTD

Magwa Crescent West

Jukskei View

Waterfall City

South Africa

8. REGISTRATION NUMBERS

TASIGNA® 200 mg capsule: 41/26/0973

TASIGNA® 150 mg capsule: 45/26/0410

NILOTINIB 150 mg NOVARTIS® 150 mg capsule: 50/26/0452

NILOTINIB 200 mg NOVARTIS® 200 mg capsule: 50/26/0453

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01 March 2013

10. DATE OF REVISION OF THE TEXT

30 June 2022

Tasigna® 150 mg	
Namibia: 14/26/0068	NS2
Botswana: BOT 1502708	S2
Tasigna® 200 mg	
Namibia: 12/26/0030	NS2
Botswana: BOT 1502707	S2

TN: 2012-PSB/GLC-0557-s; 2013-PSB/GLC-0627-s; 2013-PSB/GLC-0670-s; 2014-PSB/GLC-0676-s; 2014-PSB/GLC-0682-s, 2016-PSB/GLC-0824-s; 2017-PSB/GLC-0916-s; 2018-PSB/GLC-0954-s, 2020-PSB/GLC-1097-s