

NEW ZEALAND DATA SHEET

TASIGNA[®]

Nilotinib

150mg and 200 mg Hard Capsules

Qualitative and quantitative composition

150 mg hard capsules

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

200 mg hard capsules

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

For a full list of excipients, see List of excipients.

Pharmaceutical form

Hard capsules.

150 mg hard capsules

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

200 mg hard capsules

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

Clinical particulars

Therapeutic indications

TASIGNA is indicated for the:

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

Dosage and method of administration

Therapy should be initiated by a physician experienced in the treatment of patients with CML. TASIGNA should be taken twice daily, at approximately 12 hour intervals, and must not be taken with food. The capsules should be swallowed whole with water. No food should be consumed for at least 2 hours before the dose is taken and no additional food should be consumed for at least one hour after the dose is taken (see Special warnings and precautions for use, Interaction with other medicinal products and other forms of interaction and Pharmacokinetic properties).

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 sections Special warnings and precautions for use and Pharmacokinetic properties).

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

Dosage in patients with newly diagnosed Ph⁺ CML-CP

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

Dosage in patients with Ph+ CML-CP and CML-AP resistant to or intolerant to at least one prior therapy including imatinib

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

Monitoring recommendations and dose adjustments

A baseline ECG is recommended prior to initiating therapy with TASIGNA and should be repeated after 7 days and as clinically indicated. Hypokalaemia or hypomagnesaemia must be corrected prior to TASIGNA administration and potassium and magnesium blood levels should be monitored periodically during therapy, particularly in patients at risk for these electrolyte abnormalities (see Special warnings and precautions for use).

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 Adverse effects).

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

Table 1 Dose Adjustments for Neutropenia and Thrombocytopenia

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

*ANC = absolute neutrophil count

If clinically significant moderate or severe non-haematologic toxicity develops, dosing should be interrupted, and may be resumed at 400 mg once daily once the toxicity has resolved. If clinically appropriate, re-escalation of the dose to 300 mg (newly diagnosed Ph+ CML-CP) or 400 mg (resistant or intolerant Ph+ CML-CP and CML-AP) twice daily should be attempted. Elevated serum lipase: For Grade 3 to 4 lipase elevations, doses should be reduced to 400 mg once daily or interrupted. Serum lipase levels should be tested monthly or as clinically indicated (see Special Warnings and Precautions for use and Adverse effects).

Elevated bilirubin and hepatic transaminases: For Grade 3 to 4 bilirubin or hepatic transaminase elevations, doses should be reduced to 400 mg once daily or interrupted.

Bilirubin and hepatic transaminases levels should be tested monthly or as clinically indicated (see Adverse effects).

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

Children and adolescents

Clinical studies have not been conducted in children and adolescents.

Elderly patients

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 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 have excluded patients with serum creatinine concentration >1.5 times the upper limit of the normal range.

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

Patients with hepatic impairment

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

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 Special warnings and precautions for use).

Contraindications

Known hypersensitivity to nilotinib or to any of the excipients.

Special warnings and precautions for use

Myelosuppression

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

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 Torsade de Pointes were observed.

In the Phase II study in imatinib-resistant or intolerant CML patients in chronic and accelerated phase treated with nilotinib 400 mg twice daily, the change from baseline in mean time-averaged QTcF interval at steady state was 5 and 8 msec, respectively. QTcF of >500 msec was observed in 4 patients ($<1\%$ of these patients).

In a healthy volunteer study with exposures that were comparable to the exposures observed in patients, the time-averaged mean placebo-subtracted QTcF change from baseline was 7 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 torsade de pointes (either transient or sustained) were observed.

Significant prolongation of the QT interval may occur when TASIGNA is inappropriately taken with food, and/or strong CYP3A4 inhibitors and/or medicinal products with a known

potential to prolong QT. Therefore, co-administration with food must be avoided and concomitant use with strong CYP3A4 inhibitors and/or medicinal products with a known potential to prolong QT should be avoided (see Special warnings and precautions for use: Food Effect and Interaction with other medicinal products and other forms of interaction). The presence of hypokalaemia and hypomagnesaemia may further enhance this effect (see Dosage and method of administration).

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

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

Sudden Death

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

Drug Interactions

The administration of TASIGNA with agents that are strong CYP3A4 inhibitors and drugs that may prolong the QT interval such as anti-arrhythmic medicines should be avoided (see Dosage and method of administration and Interaction with other medicinal products and other forms of interaction). Should treatment with any of these agents be required, it is recommended that therapy with TASIGNA be interrupted if possible (see Interaction with other medicinal products and other forms of interaction). If transient interruption of treatment with TASIGNA is not possible, close monitoring of the individual for prolongation of the QT interval is indicated (see Dosage and method of administration, Interaction with other medicinal products and other forms of interaction and Pharmacokinetic properties).

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 Interaction with other medicinal products and other forms of interaction).

Food Effect

The bioavailability of nilotinib is increased by food. TASIGNA must not be taken in conjunction with food (see Dosage and method of administration and Interaction with other medicinal products and other forms of interaction) and should be taken 2 hours after a meal.

No food should be consumed for at least one hour after the dose is taken.

For patients who are unable to swallow capsules, the content of each capsule may be dispersed in one teaspoon of applesauce and should be taken immediately. Not more than one teaspoon of applesauce and no food other than applesauce must be used (see Dosage and method of administration).

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

Hepatic Impairment

Hepatic impairment has a modest effect on the pharmacokinetics of nilotinib. Single dose administration of nilotinib resulted in increases in AUC of 35%, 35% and 19% in subjects with mild, moderate and severe hepatic impairment respectively, compared to a control group of subjects with normal hepatic function. The predicted steady-state C_{max} of nilotinib showed an increase of 29%, 18% and 22% respectively. Clinical studies have excluded patients with 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. Caution is recommended in patients with hepatic impairment (see monitoring recommendations in Dosage and method of administration).

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 Dosage and method of administration).

Total gastrectomy

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

Tumor lysis syndrome

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

Lactose

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

Interaction with other medicinal products and other forms of interaction

Drugs that may increase nilotinib serum concentrations

Nilotinib is mainly metabolized in the liver, and is also a substrate for the multi-drug efflux pump, P-glycoprotein (Pgp). Therefore, absorption and subsequent elimination of systemically absorbed nilotinib may be influenced by drugs that affect CYP3A4 and/or Pgp. In a Phase I study of nilotinib given in combination with imatinib (a substrate and moderator of P-gp and CYP3A4), both drugs had a slight inhibitory effect on CYP3A4 and/or Pgp. When the two drugs were administered concomitantly, the AUC of imatinib was increased by 18% to 39%, and the AUC of nilotinib was increased by 18% to 40%.

The bioavailability of nilotinib in healthy subjects was increased by 3-fold when co-administered with the strong CYP3A4 inhibitor ketoconazole. Concurrent treatment with strong CYP3A4 inhibitors should therefore be avoided (including but not limited to ketoconazole, itraconazole, voriconazole, ritonavir, clarithromycin, and telithromycin) (see Dosage and method of administration and Special warnings and precautions for use regarding QT prolongation). Alternative concomitant medications with no or minimal CYP3A4 inhibition should be considered.

Drugs 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.

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

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.

Drugs that may have their systemic concentration altered by nilotinib

Nilotinib is identified as a competitive inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2D6 and UGT1A1 in vitro, with K_i value being lowest for CYP2C9 ($K_i=0.13$ microM). 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. In addition, single-dose administration of TASIGNA with midazolam to healthy subjects increased midazolam exposure by 30%, however the metabolic ratio of 1-hydroxy-midazolam to midazolam was not altered.

Anti-arrhythmic medicines and other drugs that may prolong QT

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 Special warnings and precautions for use).

Other interactions that may affect serum concentrations

The absorption of nilotinib is increased if it is taken with food, resulting in higher serum concentration (see Dosage and method of administration, Special warnings and precautions for use and Pharmacokinetic properties).

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

Pregnancy and lactation

Pregnancy

There are no adequate data on the use of TASIGNA in pregnant women. Studies in animals showed no teratogenicity, but embryo- and foetotoxicity was seen at doses which also showed maternal toxicity (see Preclinical safety data). TASIGNA should not be used during pregnancy unless necessary. If the drug is used during pregnancy, the patient must be informed of the potential risk to the foetus.

Women of childbearing potential

Women of childbearing potential must be advised to use effective contraception during treatment with TASIGNA.

Lactation

It is not known whether nilotinib is excreted in human milk. Studies in animals demonstrate that it is excreted into breast milk. Women should not breast-feed while taking TASIGNA, as a risk to the infant cannot be excluded.

Fertility

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 human (see Preclinical safety data).

Effects on ability to drive and use machines

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

Adverse effects

Newly diagnosed Ph+ CML-CP

The data reported below reflect exposure to TASIGNA from a randomized phase III study in newly diagnosed patients with Ph+ CML in chronic phase treated at the recommended dose of 300 mg twice daily (n=279). In this study, 87% of patients treated with nilotinib 300 mg twice daily had durations of exposure at least 12 months and 53% of patients had durations of exposure at least 18 months and 9% of patients had durations of exposure at least 24 months. The median time on treatment was 18.6 months.

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

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

In the nilotinib 300 mg twice daily group, haematologic ADRs include myelosuppression: thrombocytopenia (17%), neutropenia (15%), and anaemia (7%). See Table 3 for grade 3/4 laboratory abnormalities.

Discontinuation due to adverse events regardless of causality was observed in 7% of patients.

Resistant or intolerant Ph+ CML-CP and CML-AP

The data reported below reflect exposure to TASIGNA in 458 patients with Ph+ CML-CP (n=321) and CML-AP (n=137) resistant to or intolerant to at least one prior therapy including imatinib in an open-label multicenter study treated at the recommended dose of 400 mg twice daily. Non-haematologic adverse drug reactions (ADRs) reported with very common frequency ($\geq 10\%$ in the combined CML-CP and CML-AP patient populations) were rash, pruritus, nausea, fatigue, headache, constipation, diarrhoea, vomiting and myalgia. Most of these ADRs were mild to moderate in severity. Alopecia, muscle spasms, anorexia, arthralgia, bone pain, abdominal pain, peripheral oedema and asthenia were observed less frequently ($< 10\%$ and $\geq 5\%$) and have been of mild to moderate severity (Grade 1 or 2).

Pleural and pericardial effusions as well as complications of fluid retention occurred in $<1\%$ of patients receiving TASIGNA. Cardiac failure was observed in $<1\%$ of patients.

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

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

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

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

Most Frequently Reported Adverse Drug Reactions

Non-haematologic ADRs (excluding laboratory abnormalities) that are reported in at least 5% of the patients in TASIGNA clinical studies are shown in Table 2. These are ranked under heading of frequency, the most frequent first, using the following convention: very common ($\geq 1/10$) or common ($\geq 1/100$, $< 1/10$). The frequency is based on the highest for any TASIGNA group in the two studies.

Table 2 Most Frequently Reported Non-haematologic Adverse Drug Reactions (≥5% in any TASIGNA Group) [5,51,70,71,74,75,79]

System Organ Class	Frequency	Adverse Reaction	Newly Diagnosed Ph+ CML-CP						Resistant or Intolerant Ph+ CML-CP and CML-AP			
			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 (%)
			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	Anorexia	2	4	2	0	0	0	7	<1	<1	0
Nervous system disorders	Very common	Headache	14	22	9	1	1	0	15	1	2	<1
Gastrointestinal disorders	Very common	Nausea	14	21	34	<1	1	<1	20	<1	<1	<1
	Very common	Constipation	9	6	2	0	<1	0	12	<1	<1	0
	Very common	Diarrhoea	8	7	26	<1	0	1	11	2	2	<1
	Very Common	Vomiting	5	9	18	0	1	0	10	<1	<1	0
	Common	Abdominal pain upper	9	7	6	<1	0	<1	5	<1	<1	0
	Common	Abdominal pain	6	5	4	0	<1	0	6	<1	<1	<1
	Common	Dyspepsia	5	5	5	0	0	0	3	0	0	0
Skin and subcutaneous tissue disorders	Very common	Rash	32	37	13	<1	3	2	28	1	2	0
	Very common	Pruritus	16	13	6	<1	<1	0	24	<1	<1	0
	Very common	Alopecia	9	13	5	0	0	0	9	0	0	0
	Common	Dry Skin	8	10	5	0	0	0	5	0	0	0
	Common	Erythema	2	6	3	0	0	0	5	<1	<1	0
Musculoskeletal and connective tissue disorders	Very common	Myalgia	10	11	10	<1	0	0	10	<1	<1	<1
	Common	Arthralgia	7	9	8	<1	0	<1	7	<1	1	0
	Common	Muscle spasms	8	7	27	0	<1	<1	8	<1	<1	0

			Newly Diagnosed Ph+ CML-CP						Resistant or Intolerant Ph+ CML-CP and CML-AP			
			TASIGNA 300 mg twice daily	TASIGNA 400 mg twice daily	IMATINIB 400 mg once daily	TASIGNA 300 mg twice daily	TASIGNA 400 mg twice daily	IMATINIB 400 mg once daily	TASIGNA 400 mg twice daily			
			ALL GRADES (%)			GRADE 3 or 4 (%)			ALL GRADES (%)	GRADE 3/4 (%)	CML-CP GRADE 3/4 (%)	CML-AP GRADE 3/4 (%)
System Organ Class	Frequency	Adverse Reaction	N=279 %	N=277 %	N=280 %	N=279 %	N=277 %	N=280 %	N=458 %	N=458 %	N=321 %	N=137 %
	Common	Bone pain	4	4	3	0	0	<1	6	<1	<1	0
	Common	Pain in extremity	5	2	7	<1	<1	<1	5	<1	<1	<1
General disorders and administration site conditions	Very common	Fatigue	11	9	10	0	<1	<1	17	1	1	<1
	Common	Asthenia	9	5	8	<1	<1	0	6	0	0	0
	Common	Oedema peripheral	5	6	15	0	0	0	6	0	0	0

Additional Data from Clinical Trials

The following adverse drug reactions were reported in patients in the TASIGNA clinical studies at the recommended doses at a frequency of less than 5% (common is $\geq 1/100$ and $< 1/10$; uncommon is $> 1/1,000$ and $< 1/100$; single events are captured as Unknown in frequency. For adverse drug reactions listed under “Investigations”, very common events ($\geq 1/10$) not included in Table 2 are also reported. These adverse reactions are included based on clinical relevance and ranked in decreasing order of seriousness within each category.

Infections and Infestations: Common: folliculitis. Uncommon: upper respiratory tract infection (including pharyngitis, nasopharyngitis, rhinitis), pneumonia, bronchitis, urinary tract infection, herpes virus infection, candidiasis (including oral candidiasis), gastroenteritis. Unknown frequency: sepsis, subcutaneous abscess, anal abscess, furuncle, tinea pedis.

Neoplasms Benign, Malignant and Unspecified: Common: skin papilloma. Unknown frequency: oral papilloma.

Blood and Lymphatic System Disorders: Common: febrile neutropenia, pancytopenia, lymphopenia. Unknown frequency: thrombocythaemia, leukocytosis, eosinophilia.

Immune System Disorders: Unknown frequency: hypersensitivity.

Endocrine Disorders: Uncommon: hyperthyroidism, hypothyroidism. Unknown frequency: hyperparathyroidism secondary, thyroiditis.

Metabolism and Nutrition Disorders: Common: electrolyte imbalance (including hypomagnesaemia, hyperkalaemia, hypokalaemia, hyponatraemia, hypocalcaemia, hypophosphataemia, hypercalcaemia, hyperphosphataemia), diabetes mellitus, , hyperglycaemia hypercholesterolaemia, hyperlipidaemia, decreased appetite. Uncommon: , dehydration, increased appetite. Unknown frequency: hyperuricemia, gout, hypoglycemia, dyslipidemia,.

Psychiatric Disorders: Common: depression, insomnia, anxiety. Unknown frequency: disorientation, confusional state, amnesia, dysphoria.

Nervous System Disorders: Common: dizziness, peripheral neuropathy, hypoaesthesia, paraesthesia. Uncommon: intracranial haemorrhage, migraine, loss of consciousness (including syncope), tremor, disturbance in attention, hyperaesthesia. Unknown frequency: brain oedema, optic neuritis, lethargy, dysaesthesia, restless legs syndrome.

Eye Disorders: *Common:* eye haemorrhage, periorbital oedema, eye pruritus, conjunctivitis, dry eye. Uncommon: vision impairment, vision blurred, visual acuity reduced, eyelid oedema, photopsia, hyperaemia (scleral, conjunctival, ocular), eye irritation. Unknown frequency: papilloedema, diplopia, photophobia, eye swelling, blepharitis, eye pain, chorioretinopathy, conjunctival haemorrhage, conjunctivitis allergic, ocular surface disease.

Ear and Labyrinth Disorders: Common: vertigo. Unknown frequency: 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, pericardial effusion, coronary artery disease, cyanosis, cardiac murmur. Unknown frequency: myocardial infarction, ventricular dysfunction, pericarditis, ejection fraction decrease.

Vascular Disorders: Common: hypertension, flushing. Uncommon: hypertensive crisis, peripheral arterial occlusive disease, haematoma. Unknown frequency: shock haemorrhagic, arteriosclerosis obliterans, hypotension, thrombosis.

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. Unknown frequency: pulmonary hypertension, wheezing.

Gastrointestinal Disorders: Common: pancreatitis, abdominal discomfort, abdominal distension, dyspepsia, dysgeusia, flatulence. Uncommon: gastrointestinal haemorrhage, melaena, mouth ulceration, gastroesophageal reflux, stomatitis, oesophageal pain, dry mouth. Unknown frequency: gastrointestinal ulcer perforation, retroperitoneal haemorrhage, haematemesis, gastric ulcer, oesophagitis ulcerative, subileus, gastritis, enterocolitis, haemorrhoids, hiatus hernia, rectal haemorrhage, sensitivity of teeth, gingivitis.

Hepatobiliary Disorders: Common: hepatic function abnormal. Uncommon: hepatotoxicity, hepatitis, jaundice. Unknown frequency: cholestasis, hepatomegaly.

Skin and Subcutaneous Tissue Disorders: Common: night sweats, eczema, urticaria, erythema, hyperhidrosis, contusion, acne, dermatitis (including allergic and acneiform), dry skin. Uncommon: exfoliative rash, drug eruption, pain of skin, ecchymosis, swelling face. Unknown frequency: erythema multiforme, erythema nodosum, skin ulcer, palmar-plantar erythrodysesthesia syndrome, petechiae, photosensitivity, blister, dermal cyst, sebaceous hyperplasia, skin atrophy, skin discolouration, skin exfoliation, skin hyperpigmentation, skin hypertrophy.

Musculoskeletal and Connective Tissue Disorders: Common: musculoskeletal chest pain, musculoskeletal pain, flank pain,. Uncommon: musculoskeletal stiffness, muscular weakness, 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, gynaecomastia, erectile dysfunction. *Unknown frequency:* breast induration, menorrhagia, nipple swelling.

General Disorders and Administration Site Conditions: Common: pyrexia. chest pain (including non-cardiac chest pain), pain (including neck pain and back pain) 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: Common: haemoglobin decreased, blood amylase increased, gamma-glutamyltransferase increased, blood creatine phosphokinase increased, blood alkaline phosphatase increased, weight decreased, weight increased. Uncommon: blood lactate dehydrogenase increased, blood urea increased. Unknown frequency: troponin increased, blood bilirubin unconjugated increased, blood insulin increased, lipoprotein increased (including very low density and high density), blood parathyroid hormone increased.

Laboratories abnormalities

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

Table 3

Grade 3/4 Laboratory Abnormalities

Newly diagnosed Ph+ CML-CP			Resistant or intolerant Ph+ CML-CP	
TASIGNA 300 mg	TASIGNA 400 mg	IMATINIB 400 mg	CML-CP N=321	CML-AP N=137

	twice daily N = 279	twice daily N = 277	once daily N = 280		
Haematologic Parameters					
Myelosuppression					
-Neutropenia	12%	11%	21%	31%	42%
-Thrombocytopenia	10%	12%	9%	30%	42%
-Anaemia	4%	4%	5%	11%	27%
Biochemistry Parameters					
-Elevated creatinine	0%	0%	<1%	1%	<1%
-Elevated lipase	7%	8%	3%	18%	18%
-Elevated SGOT (AST)	1%	3%	1%	3%	2%
-Elevated SGPT (ALT)	4%	9%	3%	4%	4%
-Hypophosphataemia	5%	6%	8%	17%	15%
-Elevated Bilirubin	4%	8%	<1%	7%	9%
(total)					

Postmarketing 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 always possible to reliably estimate their frequency or establish a causal relationship to nilotinib exposure.

Frequency unknown: cases of tumor lysis syndrome have been reported in patients treated with TASIGNA.

Overdose

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.

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

Pharmacological properties

Pharmacodynamic properties

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

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

TASIGNA has little or no effect against the majority of other protein kinases examined, including Src, except for the PDGF, Kit CSF-1R, DDR and Ephrin receptor kinases which it

inhibits at concentrations within the range achieved following oral administration at therapeutic doses recommended for the treatment of CML (see Table 4).

Table 4 Kinase Profile of Nilotinib (Phosphorylation IC₅₀ nM)

Bcr-Abl	PDGFR	KIT
20	69	210

CLINICAL STUDIES

Newly diagnosed Ph+ CML-CP

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

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

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

The primary data analysis time point was when all 846 patients completed 12 months of treatment (or discontinued earlier). The median time on treatment is slightly over 18 months in all three treatment groups. In each treatment arm, more than 80% of patients had received treatment for longer than 12 months. The median actual dose intensity was 400 mg/day in the imatinib group, 593 mg/day in the nilotinib 300 mg twice daily group and 779 mg/day in the nilotinib 400 mg twice daily group. This study is on-going.

Major molecular response (MMR)

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

The primary efficacy endpoint, Major Molecular Response (MMR) rate at 12 months was statistically significantly superior in the nilotinib 300 mg twice daily group compared to the imatinib 400 mg once daily group (44.3% vs 22.3%, p<0.0001). The rate of MMR at 12 months, was also statistically significantly higher in the nilotinib 400 mg twice daily group compared to the imatinib 400 mg once daily group (42.7% vs 22.3%, p<0.0001), Table 5.

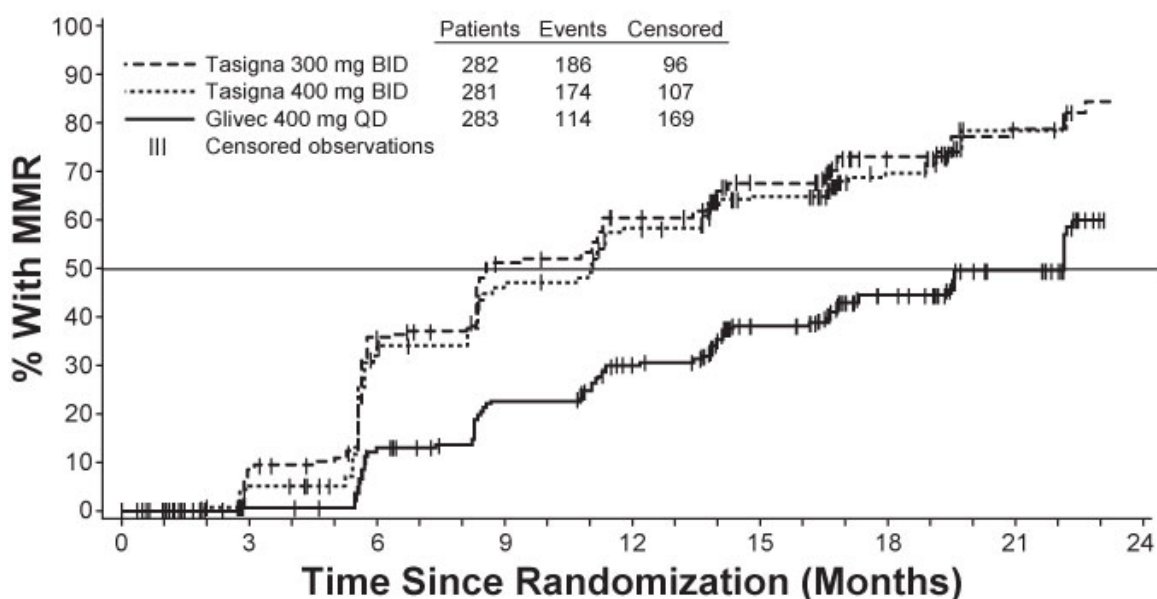
In the nilotinib recommended dose of 300 mg twice daily, the rate of MMR at 3, 6, 9 and 12 months were 8.9%, 33.0%, 43.3% and 44.3%. In the nilotinib 400 mg twice daily group, the rate of MMR at 3, 6, 9 and 12 months were 5.0%, 29.5%, 38.1% and 42.7%. In the imatinib 400 mg once daily group, the rate of MMR at 3, 6, 9 and 12 months were 0.7%, 12.0%, 18.0% and 22.3% [75]. The best overall MMR up to the cut-off date was achieved by 66.0% of patients in the nilotinib 300 mg twice daily group, 61.9% of patients in the nilotinib 400 mg twice daily group and 40.3% of patients in the imatinib group.

The Kaplan-Meier analyses of time to first MMR among all patients are graphically displayed in Figure 1. The probability of achieving MMR at different time points were higher in both

nilotinib groups compared to the imatinib group (HR=2.42 and stratified log-rank $p < 0.0001$ between nilotinib 300 mg twice daily and imatinib, HR=1.52 and stratified log-rank $p < 0.0001$ between nilotinib 400 mg twice daily and imatinib). The proportions of patients who had BCR-ABL ratios falling into categories $\leq 0.01\%$ (4-log reduction) and $\leq 0.0032\%$ (4.5 log reduction) at 12 months were statistically significantly higher in both the nilotinib groups (11.7%/4.3% and 8.5%/4.6% respectively) compared to the imatinib group (3.9%/0.4%). For all Sokal risk groups, the MMR rates at 12 months were higher in the two nilotinib groups than in the imatinib group.

Table 5 MMR rate at 12 months

	TASIGNA 300 mg twice daily N=282 n (%)	TASIGNA 400 mg twice daily N=281 n (%)	Glivec 400 mg once daily N=283 N (%)
Major Molecular Response	125(44.3)	120(42.7)	63(22.3)
95% CI for response	[38.4,50.3]	[36.8,48.7]	[17.6, 27.6]
CMH test p-value for response rate (vs. Glivec 400 mg)	<0.0001	<0.0001	

Figure 1 Kaplan-Meier estimate of time to first MMR**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 6.

Table 6 CCyR rate by 12 months [75]

	TASIGNA 300 mg twice daily N=282 n (%)	TASIGNA 400 mg twice daily N=281 n (%)	Glivec 400 mg once daily N=283 N (%)
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. Glivec 400 mg)	<0.0001	0.0005	

Progression to AP/BC on treatment

Overall by the cut-off date, 15 patients progressed to AP or BC (2 in the nilotinib 300 mg twice daily group, 1 in the nilotinib 400 mg twice daily group and 12 in the imatinib 400 mg

once daily group). No patients who progressed had achieved MMR. However, CCyR was achieved in 4 patients (all in the imatinib group). The estimated rates of patients free from progression to AP or BC at 18 months were 99.3%, 99.6% and 95.4%, respectively. There was a statistically significant difference in progression to AP or BC between nilotinib 300 mg twice daily and imatinib ($p=0.0062$) and between nilotinib 400 mg twice daily and imatinib ($p=0.0026$).

Overall survival (OS)

A total of 16 patients died during treatment or during the follow-up after discontinuation of treatment. Eight (8) of these 16 deaths were related to CML (1 in the nilotinib 300 mg twice daily group, 1 in the nilotinib 400 mg twice daily group and 6 in the imatinib 400 mg once daily group). The estimated rates of patients alive at 18 months were 98.5%, 99.3% and 96.9%, respectively. There was a statistically significant difference in OS between nilotinib 400 mg twice daily and imatinib ($p=0.0331$). Considering only CML-related deaths as events, the estimated rates of OS at 18 months were 99.6%, 99.6% and 97.6%, respectively. The Kaplan-Meier p-values for OS for CML-related deaths were 0.0572 between nilotinib 300 mg twice daily and imatinib and 0.0564 between nilotinib 400 mg twice daily and imatinib.

Resistant or intolerant Ph+ CML

An open label multicenter Phase II study was conducted to determine the efficacy of TASIGNA (400 mg twice daily) in patients with imatinib resistant or intolerant CML with separate treatment arms for chronic and accelerated phase disease. The study is ongoing. Efficacy was based on 321 CP patients and 137 AP patients enrolled. Median duration of treatment was 561 days and 264 days, respectively (see Table 7). TASIGNA was administered on a continuous basis, (twice daily 2 hours after a meal and no additional food for at least one hour) unless there was evidence of inadequate response or disease progression. Dose escalation to 600 mg twice daily was allowed.

Table 7 Duration of Exposure with TASIGNA

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

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

Overall, 73% of patients were imatinib-resistant while 27% were imatinib-intolerant. The majority of patients had a long history of CML that included extensive prior treatment with other antineoplastic agents such as imatinib, hydroxyurea, interferon, and some that had even failed stem cell transplant (Table 8). The median highest prior imatinib dose had been 600 mg/day for CP and AP patients, and the highest prior imatinib dose was >600 mg/day in 74% of all patients with 40% of patients receiving imatinib doses ≥ 800 mg/day.

Table 8 CML Disease History Characteristics

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

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

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

Chronic Phase: The MCyR rate in 321 CP patients was 59%. Most responders achieved their MCyR rapidly within 3 months (median 2.8 months) of starting TASIGNA treatment and these were sustained. The median time to achieve MCyR was just past 3 months (median 3.3 months). Of the patients who achieved MCyR, 77% (95% CI: 71% to 84%) were maintaining response at 24 months. (Median duration of MCyR has not been reached). Of the patients who achieved CCyR, 84% (95% CI: 77%-91%) were maintaining response at 24 months. Median duration of CCyR has not been reached. Patients with a CHR at baseline achieved a MCyR faster (1.4 vs. 2.8 months). Of CP patients without a baseline CHR, 76% achieved a CHR, median time to CHR was 1 month and median duration of CHR has not been reached. The estimated 24-month overall survival rate in CML -CP patients was 87%.

Accelerated Phase: The overall confirmed HR rate in 137 AP patients was 55%. Most responders achieved a HR early with TASIGNA treatment (median 1.0 months) and these have been durable (median duration of confirmed HR was 21.5 months). Of the patients who achieved HR, 49% (95% CI: 35% to 62%) were maintaining response at 24 months. MCyR rate was 32% with a median time to response of 2.8 months. Of the patients who achieved MCyR, 66% (95% CI: 50%-82%) were maintaining response at 24 months. Median duration of MCyR has not been reached. The rates of response for the two treatment arms are reported in Table 9.

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

Table 9 Response in CML

(Best Response Rate)	Chronic Phase			Accelerated Phase		
	Intolerant	Resistant	Total	Intolerant	Resistant	Total*

	(n = 95)	(n = 226)	(n = 321)	(n = 27)	(n = 109)	(n = 137)
Haematologic Response (%)						
Overall (95%CI)	-	-	-	56 (35-75)	55 (45-65)	55 (47-64)
Complete	90 (79-97)	72 (64-79)	76 ¹ (70-82)	37	30	31
NEL	-	-	-	15	11	12
Return to CP	-	-	-	4	14	12
Cytogenetic Response (%)						
Major (95%CI)	66 (56-76)	56 (49-63)	59 (54-65)	41 (22-61)	30 (22-40)	32 (24-41)
Complete	51	41	44	30	19	21
Partial	16	15	15	11	11	11

NEL = no evidence of leukaemia/marrow response

¹- 114 CP patients had a CHR at baseline and were therefore not assessable for complete haematologic response

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

Separate treatment arms were also included in the Phase II study to study TASIGNA in a group of CP and AP patients who had been extensively pre-treated with multiple therapies including a tyrosine kinase inhibitor agent in addition to imatinib. Of these patients 30/36 (83%) were treatment-resistant not intolerant. In 22 CP patients evaluated for efficacy TASIGNA induced a 32% MCyR rate and a 50% CHR rate. In 11 AP patients evaluated for efficacy, treatment induced a 36% overall HR rate.

After imatinib failure, 24 different BCR-ABL mutations were noted in 42% of chronic phase and 54% of accelerated phase CML patients who were evaluated for mutations. TASIGNA demonstrated efficacy in patients harboring a variety of BCR-ABL mutations associated with imatinib resistance, except T315I.

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 TASIGNA is given with food. Administration of TASIGNA 30 minutes or 2 hours after food increased bioavailability of nilotinib by 29% or 15%, respectively (see Dosage and method of administration, Special warnings and precautions for use and Interaction with other medicinal products and other forms of interaction). Nilotinib absorption (relative bioavailability) might be reduced by approximately 48% and 22% in patients with total gastrectomy and partial gastrectomy, respectively.

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

Distribution

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

Biotransformation

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

Elimination

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

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.

Preclinical safety data

Nilotinib has been evaluated in safety pharmacology, repeated dose toxicity, genotoxicity, reproductive toxicity, phototoxicity studies and a rat carcinogenicity study.

Nilotinib did not have effects on CNS or respiratory functions. *In vitro* cardiac safety studies demonstrated a preclinical signal for QT prolongation. No effects were seen in ECG measurements in dogs or monkeys treated up to 39 weeks or in a special telemetry study in dogs.

Repeated dose toxicity studies in dogs up to 4 weeks duration and in cynomolgus monkeys up to 9 months duration, revealed the liver as the primary target organ of toxicity of nilotinib. Alterations included increased alanine aminotransferase and alkaline phosphatase activity, and histopathology findings (mainly sinusoidal cell or Kupffer cell hyperplasia/hypertrophy, bile duct hyperplasia and periportal fibrosis). In general the changes in clinical chemistry were fully reversible after a four week recovery period, the histological alterations only showed partial reversibility. Exposures at the lowest dose levels where the liver effects were seen were lower than the exposure in humans at a dose of 800 mg/day. Only minor liver alterations were seen in mice or rats treated up to 26 weeks. Mainly reversible increases in cholesterol levels were seen in rats, dogs and monkeys. In the 2-year rat carcinogenicity study, the major target organ for non-neoplastic lesions was the uterus (dilatation, vascular ectasia, hyperplasia endothelial cell, inflammation and/or epithelial hyperplasia).

Genotoxicity 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.

There was no evidence of carcinogenicity in the 2-year rat carcinogenicity study 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 3x to 7x human daily steady state exposure (based on AUC) to nilotinib at the dose of 800mg/day.

Nilotinib did not induce teratogenicity, but did show embryo- and foetotoxicity at doses which also showed maternal toxicity. Increased postimplantation loss was observed in both

the fertility study, with treatment of both males and females, and in the embryotoxicity study with the treatment of females. Embryo-lethality and foetal effects (mainly decreased foetal weights, visceral and skeletal variations) in rats and increased resorption of foetuses and skeletal variations in rabbits were present in the embryotoxicity studies. Exposure to nilotinib in females at No-Observed-Adverse-Effect-Levels was generally less or equal to that in humans at 800 mg/day.

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

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 No-Observed-Effect-level 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.

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.

Pharmaceutical particulars

List of excipients

150 mg hard capsules

Capsule content: Lactose monohydrate; Crospovidone; Poloxamer 188; Silica colloidal, anhydrous/Colloidal silicon dioxide; Magnesium stearate

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

Printing ink: Iron oxide, black (E 172)

200 mg hard capsules

Capsule content: Lactose monohydrate; Crospovidone; Poloxamer 188; Silica colloidal, anhydrous/Colloidal silicon dioxide; Magnesium stearate

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

Printing ink: Iron oxide, red (E 172)

Incompatibilities

Not applicable.

Shelf life

150 mg hard capsules

24 months

200 mg hard capsules

36 months

Special precautions for storage and other handling

Do not store above 30°C.

Store in the original package.

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

Nature and contents of container

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

Special precautions for disposal

No special requirements.

Medicine classification

Prescription Medicine

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