ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tasigna 200 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One hard capsule contains 200 mg nilotinib (as hydrochloride monohydrate).

Excipient:
Lactose monohydrate: 156.11 mg per capsule.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tasigna is indicated for the treatment of adults with chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukaemia (CML) with resistance or intolerance to prior therapy including imatinib. Efficacy data in patients with CML in blast crisis are not available.

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the diagnosis and the treatment of patients with CML.

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

Tasigna should be taken twice daily approximately 12 hours apart and must not be taken with food. The capsules should be swallowed whole with water. No food should be consumed for 2 hours before the dose is taken and no food should be consumed for at least one hour after the dose is taken.

Tasigna may be given in combination with haematopoietic growth factors such as erythropoietin or granulocyte colony-stimulating factor (G-CSF) if clinically indicated. Tasigna may be given with hydroxyurea or anagrelide if clinically indicated.

Dose adjustments or modifications
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

Chronic phase CML at 400 mg twice daily	ANC* <1.0 x 10^9/l and/or platelet counts <50 x 10^9/l	1. Stop Tasigna, and monitor blood counts. 2. Resume within 2 weeks at prior dose if ANC >1.0 x 10^9/l and/or platelets >50 x 10^9/l. 3. If blood counts remain low, a dose reduction to 400 mg once daily may be required.
Accelerated phase CML at 400 mg twice daily	ANC* <0.5 x 10^9/l and/or platelet counts <10 x 10^9/l	1. Stop Tasigna, and monitor blood counts. 2. Resume within 2 weeks at prior dose if ANC >1.0 x 10^9/l and/or platelets >20 x 10^9/l. 3. If blood counts remain low, a dose reduction to 400 mg once daily may be required.

*ANC = absolute neutrophil count

If clinically significant moderate or severe non-haematological toxicity develops, dosing should be interrupted, and may be resumed at 400 mg once daily once the toxicity has resolved. If clinically appropriate, re-escalation of the dose to 400 mg twice daily should be considered.

Elevated serum lipase: For Grade 3-4 serum lipase elevations, doses should be reduced to 400 mg once daily or interrupted. Serum lipase levels should be tested monthly or as clinically indicated.

Elevated bilirubin and hepatic transaminases: For Grade 3-4 bilirubin 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.

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

Children and adolescents
Tasigna is not recommended for use in children and adolescents below 18 years of age due to a lack of data on safety and efficacy (see section 5.1).

Elderly patients
Approximately 30% of subjects in clinical studies were 65 years of age or over. No major differences were observed for safety and efficacy in patients ≥65 years of age as compared to adults aged 18 to 65 years.

Patients with renal impairment
Clinical studies have not been performed in patients with impaired renal function.
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 patients with hepatic impairment. However, patients with hepatic impairment should be treated with caution (see section 4.4).

Cardiac disorders
In clinical studies, patients with uncontrolled or significant cardiac disease (e.g. recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia) were excluded. Caution should be exercised in patients with relevant cardiac disorders (see section 4.4).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Myelosuppression
Treatment with Tasigna is associated with (National Cancer Institute Common Toxicity Criteria grade 3-4) thrombocytopenia, neutropenia and anaemia. Occurrence is more frequent in patients with accelerated-phase CML. Complete blood counts should be performed every two weeks for the first 2 months and then monthly thereafter, or as clinically indicated. Myelosuppression was generally reversible and usually managed by withholding Tasigna temporarily or dose reduction (see section 4.2).

QT prolongation
Tasigna has been shown to prolong cardiac ventricular repolarisation as measured by the QT interval on the surface ECG in a concentration-dependent manner.

In the Phase II study in imatinib-resistant and intolerant CML patients in chronic and accelerated phase, 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 <1% of these patients. No episodes of torsade de pointes were observed in clinical studies.

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. Additionally, no clinically relevant arrhythmias were observed during the conduct of the trial. In particular, no episodes of torsade de pointes (transient or sustained) were observed.

Significant prolongation of the QT interval may occur when nilotinib is inappropriately taken with strong CYP3A4 inhibitors and/or medicinal products with a known potential to prolong QT, and/or food (see section 4.5). The presence of hypokalaemia and hypomagnesaemia may further enhance this effect. Prolongation of the QT interval may expose patients to the risk of fatal outcome.

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 congenital long QT prolongation
- with uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia.
- taking anti-arrhythmic medicinal products or other substances that lead to QT prolongation.

Close monitoring for an effect on the QTc interval is advisable and a baseline ECG is recommended prior to initiating therapy with Tasigna and as clinically indicated. Hypokalaemia or hypomagnesaemia must be corrected prior to Tasigna administration and should be monitored periodically during therapy.

Sudden death
Uncommon cases (0.1 to 1%) of sudden deaths have been reported in patients receiving Tasigna with a past medical history of cardiac disease or significant cardiac risk factors. Co-morbidities in addition to the underlying malignancy were also frequently present as were concomitant medications. Ventricular repolarisation abnormalities may have been contributory factors.

Interactions with other medicinal products
The administration of Tasigna with agents that are strong CYP3A4 inhibitors (including, but not limited to, ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, ritonavir) should be avoided. Should treatment with any of these agents be required, it is recommended that therapy

with Tasigna be interrupted if possible (see section 4.5). If transient interruption of treatment with Tasigna is not possible, close monitoring of the individual for prolongation of the QT interval is indicated (see sections 4.2, 4.5 and 5.2).

Concomitant use of Tasigna with medicinal products that are potent inducers of CYP3A4 (e.g. phenytoin, rifampicin, carbamazepine, phenobarbital and St. John's Wort) is likely to reduce exposure to nilotinib to a clinically relevant extent. Therefore, in patients receiving Tasigna, coadministration of alternative therapeutic agents with less potential for CYP3A4 induction should be selected (see section 4.5).

Food effect
The bioavailability of nilotinib is increased by food. Tasigna should not be taken in conjunction with food (see sections 4.2 and 4.5) and should be taken 2 hours after a meal. No food should be consumed for at least one hour after the dose is taken. Grapefruit juice and other foods that are known to inhibit CYP3A4 should be avoided.

Hepatic impairment
Hepatic impairment has a modest effect on the pharmacokinetics of nilotinib. Single dose administration of 200 mg of nilotinib resulted in increases in AUC of 35%, 35% and 19% in subjects with mild, moderate and severe hepatic impairment, respectively, compared to a control group of subjects with normal hepatic function. The predicted steady-state C_{max} of nilotinib showed an increase of 29%, 18% and 22%, respectively. Clinical studies have excluded patients with alanine transaminase (ALT) and/or aspartate transaminase (AST) >2.5 (or >5, if related to disease) times the upper limit of the normal range and/or total bilirubin >1.5 times the upper limit of the normal range. Metabolism of nilotinib is mainly hepatic. Patients with hepatic impairment might therefore have increased exposure to nilotinib and should be treated with caution (see section 4.2).

Serum lipase
Elevation in serum lipase has been observed. Caution is recommended in patients with previous history of pancreatitis.

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

Lactose
Tasigna capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Substances that may increase nilotinib serum concentrations
Nilotinib is mainly metabolised in the liver and is also a substrate for the multi-drug efflux pump, P-glycoprotein (P-gp). Therefore, absorption and subsequent elimination of systemically absorbed nilotinib may be influenced by substances that affect CYP3A4 and/or P-gp. Concomitant administration of nilotinib with imatinib (a substrate and moderator of P-gp and CYP3A4), had a slight inhibitory effect on CYP3A4 and/or P-gp. The AUC of imatinib was increased by 18% to 39%, and the AUC of nilotinib was increased by 18% to 40%. These changes are unlikely to be clinically important.

The exposure to nilotinib in healthy subjects was increased 3-fold when co-administered with the strong CYP3A4 inhibitor ketoconazole. Concomitant treatment with strong CYP3A4 inhibitors, including ketoconazole, itraconazole, voriconazole, ritonavir, clarithromycin, and telithromycin, should therefore be avoided (see sections 4.2 and 4.4). Increased exposure to nilotinib might also be expected with moderate CYP3A4 inhibitors. Alternative concomitant medications with no or minimal CYP3A4 inhibition should be considered.

Substances that may decrease nilotinib serum concentrations
Rifampicin, a potent CYP3A4 inducer, decreases nilotinib C_{max} by 64% and reduces nilotinib AUC by 80%. Rifampicin and nilotinib should not be used concomitantly.

The concomitant administration of other medicinal products that induce CYP3A4 (e.g. phenytoin, carbamazepine, phenobarbital and St. John's Wort) is likewise likely to reduce exposure to nilotinib to a clinically relevant extent. In patients for whom CYP3A4 inducers are indicated, alternative agents with less enzyme induction potential should be selected.

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.

Substances that may have their systemic concentration altered by nilotinib
Nilotinib is a relatively strong inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2D6 and UGT1A1 *in vitro*, with Ki value being lowest for CYP2C9 (Ki=0.13 microM).

A single-dose drug-drug interaction study in healthy volunteers with 25 mg warfarin, a sensitive CYP2C9 substrate, and 800 mg nilotinib did not result in any changes in warfarin pharmacokinetic parameters or warfarin pharmacodynamics measured as prothrombin time (PT) and international normalised ratio (INR). There are no steady-state data. This study suggests that a clinically meaningful drug-drug interaction between nilotinib and warfarin is less likely up to a dose of 25 mg of warfarin. Due to lack of steady-state data, control of warfarin pharmacodynamic markers (INR or PT) following initiation of nilotinib therapy (at least during the first 2 weeks) is recommended.

In addition, single-dose administration of Tasigna with orally administered midazolam to healthy subjects increased midazolam exposure by 30%. It cannot be excluded that the effect of nilotinib is greater at steady state. Caution should be exercised when co-administering Tasigna with substrates of these enzymes that have a narrow therapeutic index [e.g. astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil or ergot alkaloids (ergotamine, dihydroergotamine)].

Anti-arrhythmic medicinal products and other substances that may prolong QT
Nilotinib should be used with caution in patients who have or may develop prolongation of QT, including those patients taking anti-arrhythmic medicinal products such as amiodarone, disopyramide, procainamide, quinidine and sotalol or other medicinal products that may lead to QT prolongation such as chloroquine, halofantrine, clarithromycin, haloperidol, methadone and moxifloxacin (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 sections 4.2, 4.4 and 5.2). Grapefruit juice and other foods that are known to inhibit CYP3A4 should be avoided.

4.6 Pregnancy and lactation

Pregnancy
There are no data on the use of Tasigna in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Tasigna should not be used during pregnancy unless clearly necessary. If it is used during pregnancy, the patient must be informed of the potential risk to the foetus.

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 milk. Women should not breast-feed during treatment with Tasigna, as a risk to the infant cannot be excluded.

4.7 Effects on ability to drive and use machines

No studies on the effects of nilotinib on the ability to drive and use machines have been performed. Patients experiencing dizziness, fatigue, visual impairment or other undesirable effects with a potential impact on the ability to drive or use machines safely should refrain from these activities as long as the undesirable effects persist (see section 4.8).

4.8 Undesirable effects

The data described below reflect exposure to Tasigna in 458 patients in an open-label multicentre Phase II study in patients with imatinib-resistant or intolerant CML in chronic phase (n=321) and accelerated phase (n=137) treated at the recommended dose of 400 mg twice daily. The median duration of exposure in days was 561 (1-1,096) for the CML-CP patients and 264 (2-1,160) for the CML-AP patients.

The most frequent non-haematological drug-related adverse events were rash, pruritus, nausea, fatigue, headache, abdominal pain, constipation and diarrhoea. Most of these adverse events were mild to moderate in severity. Vomiting, myalgia, alopecia, muscle spasms, anorexia, arthralgia, bone pain, peripheral oedema and asthenia were observed commonly and have been of mild to moderate severity (Grade 1 or 2). Discontinuation for drug-related adverse reactions was observed in 16% of CP and 10% of AP patients.

Treatment emergent haematological toxicities include myelosuppression: thrombocytopenia (31%), neutropenia (17%) and anaemia (14%). 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 were reported in 1% and <1% of patients, respectively.

QTcF exceeding 500 msec was observed in <1% of patients. No episodes of torsade de pointes (transient or sustained) were observed.

Non-haematological adverse reactions (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 using the following convention: very common (≥1/10) or common (≥1/100 to <1/10). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 2 Non-haematological adverse reactions (≥5% of all patients, n=458)

System organ class	Frequency	Adverse reaction	All grades n=458 %	Grade 3-4 n=458 %	Chronic phase Grade 3-4 n=321 %	Accelerated phase Grade 3-4 n=137 %
Metabolism and nutrition disorders	Common	Anorexia	7	<1	<1	0
Nervous system disorders	Very common	Headache	15	1	2	<1
Gastrointestinal disorders	Very common	Nausea	20	<1	<1	<1
	Very common	Constipation	12	<1	<1	0
	Very common	Diarrhoea	11	2	2	<1
	Common	Vomiting	10	<1	<1	0
	Common	Abdominal pain	6	<1	<1	<1
	Common	Abdominal pain upper	5	<1	<1	0
Skin and subcutaneous tissue disorders	Very common	Rash	28	1	2	0
	Very common	Pruritus	24	<1	<1	0
	Common	Alopecia	9	0	0	0
	Common	Dry Skin	5	0	0	0
	Common	Erythema	5	<1	<1	0
Musculoskeletal and connective tissue disorders	Common	Myalgia	10	<1	<1	<1
	Common	Arthralgia	7	<1	1	0
	Common	Muscle spasms	8	<1	<1	0
	Common	Bone pain	6	<1	<1	0
	Common	Pain in extremity	5	<1	<1	<1
General disorders and administration site conditions	Very common	Fatigue	17	1	1	<1
	Common	Asthenia	6	<1	0	<1
	Common	Oedema peripheral	6	0	0	0

The following adverse reactions were reported in patients in the Tasigna clinical studies at a frequency of less than 5% (common is ≥1/100 to <1/10; uncommon is >1/1,000 to <1/100; single events are captured as frequency not known [cannot be estimated from the available data]). For laboratory abnormalities, very common events (≥1/10) not included in Table 2 are also reported. These adverse reactions are included based on clinical relevance and ranked in order of decreasing seriousness within each category.

Infections and infestations:
Uncommon: pneumonia, urinary tract infection, gastroenteritis, upper respiratory tract infection, bronchitis, herpes virus infection, candidiasis.
Not known: sepsis.

Blood and lymphatic system disorders:
Common: febrile neutropenia, pancytopenia.
Uncommon: thrombocythaemia, leukocytosis.

Endocrine disorders:
Uncommon: hyperthyroidism, hypothyroidism.
Not known: thyroiditis.

Metabolism and nutrition disorders:
Common: electrolyte imbalance (including hypomagnesaemia, hyperkalaemia, hypokalaemia, hyponatraemia, hypocalcaemia, hypophosphataemia, hypercalcaemia, hyperphosphataemia), hyperglycaemia.
Uncommon: dehydration, decreased appetite, increased appetite.
Not known: diabetes mellitus.

Psychiatric disorders:
Common: depression, insomnia.
Uncommon: anxiety.
Not known: disorientation, confusional state.

Nervous system disorders:
Common: dizziness, paraesthesia.
Uncommon: hypoaesthesia, intracranial haemorrhage, loss of consciousness (including syncope), migraine, tremor, disturbance in attention, hyperaesthesia.
Not known: brain oedema, optic neuritis, peripheral neuropathy.

Eye disorders:
Common: eye haemorrhage, periorbital oedema, conjunctivitis, dry eye.
Uncommon: visual impairment, vision blurred, visual acuity reduced, eye irritation.
Not known: papilloedema, diplopia, photophobia, eye swelling, blepharitis, eye pain.

Ear and labyrinth disorders:
Common: vertigo.
Not known: hearing impaired, ear pain, tinnitus.

Cardiac disorders:
Common: angina pectoris, arrhythmia (including atroventricular block, cardiac flutter, extrasystoles, tachycardia, atrial fibrillation, bradycardia), palpitations, electrocardiogram QT prolonged.
Uncommon: cardiac failure, pericardial effusion, coronary artery disease, cardiac murmur.
Not known: myocardial infarction, ventricular dysfunction, pericarditis.

Vascular disorders:
Common: hypertension, flushing.
Uncommon: hypertensive crisis, haematoma.
Not known: shock haemorrhagic, 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.
Not known: pulmonary hypertension, wheezing.

Gastrointestinal disorders:
Common: pancreatitis, abdominal discomfort, abdominal distension, dyspepsia, flatulence.
Uncommon: gastrointestinal haemorrhage, melaena, mouth ulceration, gastroesophageal reflux, stomatitis, dry mouth.
Not known: gastrointestinal ulcer perforation, retroperitoneal haemorrhage, haematemesis, gastric ulcer, oesophagitis ulcerative, subileus.

Hepatobiliary disorders:
Uncommon: hepatitis.
Not known: cholestasis, hepatotoxicity, hepatomegaly, jaundice.

Skin and subcutaneous tissue disorders:
Common: night sweats, eczema, urticaria, erythema, hyperhidrosis, dermatitis, dry skin.
Uncommon: exfoliative rash, ecchymosis, swelling face.
Not known: erythema nodosum, skin ulcer, drug eruption, palmar-plantar erythrodysaesthesia syndrome, petechiae, photosensitivity.

Musculoskeletal and connective tissue disorders:
Common: musculoskeletal chest pain, musculoskeletal pain.
Uncommon: flank pain, musculoskeletal stiffness, muscular weakness, joint swelling.
Not known: arthritis.

Renal and urinary disorders:
Common: pollakiuria.
Uncommon: dysuria, micturition urgency, nocturia.
Not known: renal failure, haematuria, urinary incontinence.

Reproductive system and breast disorders:
Uncommon: breast pain, gynaecomastia, erectile dysfunction.

General disorders and administration site conditions:
Common: chest pain, pain (including neck pain and back pain), pyrexia, malaise.
Uncommon: face oedema, gravitational oedema, influenza-like illness, chills.

Investigations:
Common: blood amylase increased, blood alkaline phosphatase increased, gamma-glutamyltransferase increased, blood creatinine phosphokinase increased, weight decreased, weight increased.
Uncommon: blood lactate dehydrogenase increased, blood glucose decreased, blood urea increased.

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

Table 3 Grade 3-4 laboratory abnormalities

	CML-CP n=321 %	**CML-AP n=137 %**
	Grade 3-4	**Grade 3-4**
Haematological parameters		
Myelosuppression		
- Neutropenia	31%	42%
- Thrombocytopenia	30%	42%
- Anaemia	11%	27%
Biochemistry parameters		
- Elevated creatinine	1%	<1%
- Elevated lipase	18%	18%
- Elevated SGOT (AST)	3%	2%
- Elevated SGPT (ALT)	4%	4%
- Hypophosphataemia	17%	15%
- Elevated bilirubin (total)	7%	9%

Sudden death
Uncommon cases (0.1 to 1%) of sudden deaths have been reported in Tasigna clinical trials and/or compassionate use programs in patients with a past medical history of cardiac disease or significant cardiac risk factors (see section 4.4).

4.9 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 medicinal products. 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: Protein-kinase inhibitors, ATC code: L01XE08

Tasigna is a potent 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 substance 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 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 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 IC_{50} nM)

Bcr-Abl	PDGFR	KIT
20	69	210

Clinical studies

An open-label, uncontrolled, multicentre Phase II study was conducted to determine the efficacy of Tasigna 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 for CP patients and 264 days for AP patients (see Table 5). Tasigna was administered on a continuous basis (twice daily 2 hours after a meal and with no food for at least one hour after administration) unless there was evidence of inadequate response or disease progression. Dose escalation to 600 mg twice daily was allowed.

Table 5 Duration of exposure with Tasigna

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

Resistance to imatinib included failure to achieve a complete haematological response (by 3 months), cytogenetic response (by 6 months) or major cytogenetic response (by 12 months) or progression of disease after a previous cytogenetic or haematological response. Imatinib intolerance included patients who discontinued imatinib because of toxicity and 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, including imatinib, hydroxyurea, interferon, and some had even failed organ transplant (Table 6). The median highest prior imatinib dose had been 600 mg/day. 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 6 CML disease history characteristics

	Chronic phase (n=321)	Accelerated phase (n=137)*
Median time since diagnosis in months (range)	58 (5–275)	71 (2–298)
Imatinib Resistant Intolerant without MCyR	 226 (70%) 95 (30%)	 109 (80%) 27 (20%)
Median time of imatinib treatment in days (25th-75th percentiles)	975 (519-1,488)	857 (424-1,497)
Prior hydroxyurea	83%	91%
Prior interferon	58%	50%
Prior bone marrow transplant	7%	8%

* Missing information on imatinib-resistant/intolerant status for one patient.

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

Chronic Phase
The MCyR rate in 321 CP patients was 51%. 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 CCyR was just past 3 months (median 3.4 months). Of the patients who achieved MCyR, 77% (95% CI: 70% - 84%) were maintaining response at 24 months. Median duration of MCyR has not been reached. Of the patients who achieved CCyR, 85% (95% CI: 78% - 93%) were maintaining response at 24 months. Median duration of CCyR has not been reached. Patients with a CHR at baseline achieved a MCyR faster (1.9 vs. 2.8 months). Of CP patients without a baseline CHR, 70% achieved a CHR, median time to CHR was 1 month and median duration of CHR was 32.8 months. 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 50%. Most responders achieved a HR early with Tasigna treatment (median 1.0 months) and these have been durable (median duration of confirmed HR was 24.2 months). Of the patients who achieved HR, 53% (95% CI: 39% - 67%) were maintaining response at 24 months. MCyR rate was 30% with a median time to response of 2.8 months. Of the patients who achieved MCyR, 63% (95% CI: 45% - 80%) were maintaining response at 24 months. Median duration of MCyR was 32.7 months. The estimated 24-month overall survival rate in CML-AP patients was 70%.

The rates of response for the two treatment arms are reported in Table 7.

Table 7 Response in CML

(Best Response Rate)	**Chronic Phase**			**Accelerated Phase**		
	Intolerant (n=95)	**Resistant (n=226)**	**Total (n=321)**	**Intolerant (n=27)**	**Resistant (n=109)**	**Total* (n=137)**
Haematological Response (%)						
Overall (95%CI)	-	-	-	48 (29-68)	51 (42-61)	50 (42-59)
Complete	87 (74-94)	65 (56-72)	70[1] (63-76)	37	28	30
NEL	-	-	-	7	10	9
Return to CP	-	-		4	13	11
Cytogenetic Response (%)						
Major (95%CI)	57 (46-67)	49 (42-56)	51 (46-57)	33 (17-54)	29 (21-39)	30 (22-38)
Complete	41	35	37	22	19	20
Partial	16	14	15	11	10	10

NEL = no evidence of leukaemia/marrow response
[1] 114 CP patients had a CHR at baseline and were therefore not assessable for complete haematological response
* Missing information on imatinib-resistant/intolerant status for one patient.

Efficacy data in patients with CML-BC are not yet available. Separate treatment arms were also included in the Phase II study to investigate 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. The study is ongoing. 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.

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 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 sections 4.2, 4.4 and 4.5). Nilotinib absorption (relative bioavailability) might be reduced by approximately 48% and 22% in patients with total gastrectomy and partial gastrectomy, respectively.

Distribution
The blood-to-plasma ratio of nilotinib is 0.71. 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.

Elimination
After a single dose of radiolabelled nilotinib in healthy subjects, more than 90% of the dose was eliminated within 7 days, mainly in faeces (94% of the dose). 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 with 400 mg twice-daily dosing at steady state was 35% higher than with 800 mg once-daily dosing. 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 pharmacokinetics with daily dosing was approximately 17 hours. Inter-patient variability in nilotinib pharmacokinetics was moderate to high.

5.3 Preclinical safety data

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

Nilotinib did not have effects on CNS or respiratory functions. *In vitro* cardiac safety studies demonstrated a preclinical signal for QT prolongation, based upon block of hERG currents and prolongation of the action potential duration in isolated rabbit hearts by nilotinib. No effects were seen in ECG measurements in dogs or monkeys treated for up to 39 weeks or in a special telemetry study in dogs.

Repeated-dose toxicity studies in dogs of up to 4 weeks' duration and in cynomolgus monkeys of 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 and the histological alterations showed partial reversibility. Exposures at the lowest dose levels at which 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 for up to 26 weeks. Mainly reversible increases in cholesterol levels were seen in rats, dogs and monkeys.

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.

Nilotinib did not induce teratogenicity, but did show embryo- and foetotoxicity at doses that also showed maternal toxicity. Increased post-implantation loss was observed in both the fertility study, which involved treatment of both males and females, and the embryotoxicity study, which involved treatment of females. Embryo-lethality and foetal effects (mainly decreased foetal weights, premature fusion of the facial bones (fused maxilla/zygomatic) visceral and skeletal variations) in rats and increased resorption of foetuses and skeletal variations in rabbits were present in the embryotoxicity studies. In a pre- and postnatal development study in rats, maternal exposure to nilotinib caused reduced pup body weight with associated changes in physical development parameters as well as reduced mating and fertility indices in the offspring. Exposure to nilotinib in females at No-Observed-Adverse-Effect-Levels was generally less or equal to that in humans at 800 mg/day.

No effects on sperm count/motility or on fertility were noted in male and female rats up to the highest tested dose, approximately 5 times the recommended dosage for humans.

Nilotinib was shown to absorb light in the UV-B and UV-A range, is distributed into the skin and showed a phototoxic potential *in vitro*, but no effects have been observed *in vivo*. Therefore the risk that nilotinib causes photosensitisation in patients is considered very low.

Carcinogenicity studies with nilotinib have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

Capsule shell:
Gelatin
Titanium dioxide (E171)
Yellow iron oxide (E172)

Printing ink:
Shellac
Red iron oxide (E172)
Soya lecithin (E322)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/PVDC/Al and PA/Al/PVC/Al blisters.

Tasigna is available in weekly and monthly packs:
- The weekly pack contains 28 capsules.
- The monthly pack contains 112 capsules (4x28). A monthly pack consists of 4 individual weekly wallets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/422/001-004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19.11.2007

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

The MAH shall ensure that prior to launch, all doctors who intend to prescribe Tasigna, and all pharmacists who may dispense Tasigna, are provided with a healthcare professional information pack containing the following:

- Educational brochure
- Summary of Product Characteristics (SPC) and Package Leaflet and Labelling

Key elements to be included in the educational brochure

- Brief background on Tasigna, its authorised indication and posology
- Information on the cardiac risks associated with the use of Tasigna
    - That Tasigna can cause prolongation of the QT interval and that patients at risk of arrythmia, especially torsade de pointes, should not be prescribed Tasigna.
    - The need to avoid co-prescription with any other medicines that might prolong the QT interval
    - Caution in prescribing to patients with a history of or risk factors for coronary heart disease
    - That Tasigna may cause fluid retention, cardiac failure and pulmonary oedema

- That Tasigna is metabolised by CYP3A4 and that strong inhibitors or inducers of this enzyme may significantly affect exposure to Tasigna.
    - That inhibitors may increase the potential for adverse drug reactions in particular QT interval prolongation.
    - To warn patients about OTC medicines in particular St John's Wort

- The need to inform patients about the effects of food on Tasigna
    - Not to eat within two hours before and one hour after taking Tasigna
    - The need to avoid foods such as grapefruit juice which inhibit CYP3A4 enzymes

- **OTHER CONDITIONS**

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, as described in version 8.0 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 6 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, any updated RMP should be submitted at the same time as the following Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:
- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMEA

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF WEEKLY PACK

1. NAME OF THE MEDICINAL PRODUCT

Tasigna 200 mg hard capsules
Nilotinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One hard capsule contains 200 mg nilotinib (as hydrochloride monohydrate).

3. LIST OF EXCIPIENTS

Contains lactose – see the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/422/001 PVC/PVDC/Al
EU/1/07/422/002 PA/Al/PVC/Al

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tasigna 200 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

Tasigna 200 mg hard capsules
Nilotinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF MONTHLY PACK

1. NAME OF THE MEDICINAL PRODUCT

Tasigna 200 mg hard capsules
Nilotinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One hard capsule contains 200 mg nilotinib (as hydrochloride monohydrate).

3. LIST OF EXCIPIENTS

Contains lactose – see the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

112 hard capsules
Monthly pack containing 4 wallets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/422/003 PVC/PVDC/Al
EU/1/07/422/004 PA/Al/PVC/Al

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tasigna 200 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE WALLET OF MONTHLY PACK

1. NAME OF THE MEDICINAL PRODUCT

Tasigna 200 mg hard capsules
Nilotinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One hard capsule contains 200 mg nilotinib (as hydrochloride monohydrate).

3. LIST OF EXCIPIENTS

Contains lactose – see the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 hard capsules
Component of a monthly pack containing 4 wallets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/422/003 PVC/PVDC/Al
EU/1/07/422/004 PA/Al/PVC/Al

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tasigna 200 mg

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Tasigna 200 mg hard capsules
Nilotinib

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT TASIGNA IS AND WHAT IT IS USED FOR

What Tasigna is
Tasigna is a medicine containing an active substance called nilotinib.

What Tasigna is used for
Tasigna is used to treat a type of leukaemia called Philadelphia chromosome positive chronic myeloid leukaemia (Ph-positive CML). CML is a cancer of the blood which makes the body produce too many abnormal white blood cells.

Tasigna is used in patients with CML who are no longer benefiting from previous treatment including imatinib. It is also used in patients who experienced serious side effects with previous treatment and are not able to continue taking it.

How Tasigna works
In patients with CML, a change in DNA (genetic material) triggers a signal that tells the body to produce abnormal white blood cells. Tasigna blocks this signal, and thus stops the production of these cells.

Monitoring your Tasigna treatment
You will have regular tests, including blood tests, during treatment. These will monitor the amount of blood cells (white blood cells, red blood cells and platelets) in your body to see how Tasigna is tolerated.

If you have any questions about how Tasigna works or why it has been prescribed for you, ask your doctor.

2. BEFORE YOU TAKE TASIGNA

Follow all the doctor's instructions carefully. They may differ from the general information contained in this leaflet.

Do not take Tasigna
- if you are **allergic** (hypersensitive) to nilotinib or any of the other ingredients of Tasigna listed at the end of this leaflet.

If you think you may be allergic, tell your doctor **before taking Tasigna**.

Take special care with Tasigna
- if you have a **heart disorder**, such as an abnormal electrical signal called "prolongation of the QT interval".
- if you are being **treated with medicines** that affect the heart beat (anti-arrhythmics) or the liver (see **Taking other medicines**).
- if you suffer from lack of potassium or magnesium.
- if you have been treated with a medicine of the type called anthracyclines (frequently used in leukaemia therapy).
- if you have a liver or pancreas disorder.

If any of these apply to you, tell your doctor.

During treatment with Tasigna
- if you faint (loss of consciousness) or have an irregular heart beat while taking Tasigna, **tell your doctor immediately** as this may be a sign of a serious heart condition. Prolongation of the QT interval or an irregular heart beat may lead to sudden death. Uncommon cases of sudden death have been reported in patients taking Tasigna.

Taking other medicines
Tasigna may interfere with some other medicines.

Tell your doctor or pharmacist **before taking Tasigna** if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This includes in particular:
- antiarrhythmics – used to treat irregular heart beat;
- chloroquine, halofantrine, clarithromycin, haloperidol, methadone - medicines that may have an unwanted effect on the function of the heart;
- ketoconazole, itraconazole, voriconazole, moxifloxacin, clarithromycin, telithromycin – used to treat infections;
- ritonavir – a medicine from the class " antiproteases" used to treat HIV;
- carbamazepine, phenobarbital, phenytoin – used to treat epilepsy;
- rifampicin – used to treat tuberculosis;
- St. John's Wort – a herbal product used to treat depression and other conditions (also known as *Hypericum perforatum*);
- midazolam – used to relieve anxiety before surgery;
- warfarin – used to treat blood coagulation disorders (such as blood clots or thromboses);
- astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil or ergot alkaloids (ergotamine, dihydroergotamine).

These medicines should be avoided during your treatment with Tasigna. If you are taking any of these, your doctor might prescribe other alternative medicines.

You should also tell your doctor **if you are already taking Tasigna** and you are prescribed a new medicine that you have not taken previously during Tasigna treatment.

Taking Tasigna with food and drink
- **Do not take Tasigna with food.** Take the capsules at least 2 hours after any food and then wait at least 1 hour before eating again. For more information, see under "When to take Tasigna" in section 3.
- Do not drink grapefruit juice or eat grapefruit. It may increase the amount of Tasigna in the blood, possibly to a harmful level.

Older people (age 65 years and over)
Tasigna can be used by people aged 65 years and over at the same dose as for other adults.

Pregnancy and breast-feeding
- **Tasigna is not recommended during pregnancy** unless clearly necessary. If you are pregnant or think that you may be, tell your doctor who will discuss with you whether you can take Tasigna during your pregnancy.
- **Women who might get pregnant** are advised to use effective contraception during treatment.
- **Breast-feeding is not recommended** during treatment with Tasigna. Tell your doctor if you are breast-feeding.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
If you experience side effects (such as dizziness or visual disorders) with a potential impact on the ability to safely drive or use any tools or machines after taking Tasigna, you should refrain from these activities until the effect has disappeared.

Important information about some of the ingredients of Tasigna
This medicine contains lactose (also known as milk sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE TASIGNA

Always take Tasigna exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

How much Tasigna to take
- The starting dose is 800 mg per day. This dose is achieved by taking two capsules of 200 mg twice a day.

When to take Tasigna
Take the capsules:
- twice a day (approximately every 12 hours);
- at least 2 hours after any food;
- then wait 1 hour before eating again.

If you have questions about when to take Tasigna, talk to your doctor or pharmacist. Taking Tasigna at the same time each day will help you remember when to take your capsules.

How to take Tasigna
- Swallow the capsules whole with water.
- Do not open the capsules.
- Do not take any food together with the capsules.

How long to take Tasigna
Continue taking Tasigna every day for as long as your doctor tells you. This is a long-term treatment. Your doctor will regularly monitor your condition to check that the treatment is having the desired effect.

If you have questions about how long to take Tasigna, talk to your doctor.

If you take more Tasigna than you should
If you have taken more Tasigna than you should have, or if someone else accidentally takes your capsules, contact a doctor or hospital for advice straight away. Show them the pack of capsules and this package leaflet. Medical treatment may be necessary.

If you forget to take Tasigna
If you miss a dose, take your next dose as scheduled. Do not take a double dose to make up for the forgotten capsules.

If you stop taking Tasigna
Do not stop taking Tasigna unless your doctor tells you to.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Tasigna can cause side effects, although not everybody gets them. Most of the side effects are mild to moderate and will generally disappear after a few days to a few weeks of treatment.

Some side effects could be serious.
These side effects are common, uncommon or have been reported in very few patients.
- rapid weight gain, swelling of hands, ankles, feet or face
- chest pain, high blood pressure, irregular heart rhythm (signs of heart disorders)
- difficulty breathing, cough, wheezing, swelling of the feet or legs (signs of lung disorders)
- fever, sore throat, mouth sores, weakness, bruising, frequent infections (signs of blood disorders)
- weakness or paralysis of the limbs or face, difficulty speaking, severe headache, seeing, feeling or hearing things that are not there (signs of nervous system disorders)
- thirst, dry skin, irritability, dark urine, decreased urine output (signs of kidney disorders)
- blurred vision, loss of vision, visible bleeding in white of eye (signs of eye disorders)
- swelling and pain in one part of the body (signs of clotting within a vein)
- abdominal pain, nausea, vomiting of blood, black stools, constipation, swollen abdomen (signs of gastrointestinal disorders)
- severe upper abdominal pain (sign of pancreatitis)
- yellow skin and eyes, nausea, loss of appetite, light-coloured urine (signs of liver disorders)
- rash, painful red lumps, pain in joints and muscles (signs of skin disorders)
- excessive thirst, high urine output, increased appetite with weight loss, tiredness (signs of high level of sugar in the blood)
- fast heartbeat, bulging eyes, weight loss, swelling at the front of the neck (signs of overactive thyroid gland)

If you get any of these, **tell your doctor straight away**.

Some side effects are very common.
These effects may affect more than 10 in every 100 patients.
- nausea, constipation, diarrhoea
- headache
- tiredness
- itching, rash

If any of these affects you severely, tell your doctor.

Some side effects are common.
These effects may affect between 1 and 10 in every 100 patients.
- vomiting, stomach discomfort after meals, flatulence, swelling or bloating of the abdomen
- bone pain, pain in joints, muscle spasms, muscle pain
- pain including back pain, neck pain and pain in extremity
- eye irritation, swelling, discharge, itching or redness, dry eye (signs of eye disorders)
- skin reddening, dry skin
- loss of appetite, weight decrease or increase
- hair loss
- insomnia, depression
- night sweats, excessive sweating, hot flushes
- dizziness, generally feeling unwell; spinning sensation
- tingling or numbness
- voice disorder
- nose bleed
- frequent urine output
- palpitations (sensation of rapid heart beat)

If any of these affects you severely, tell your doctor.

Some side effects are uncommon.
These effects may affect less than 1 in every 100 patients.
- decreased or increased skin sensitivity
- dry mouth
- heartburn
- breast pain
- increased appetite
- anxiety, attention disorder
- difficulty and pain when urinating, exaggerated sense of needing to urinate
- inability to achieve or maintain an erection
- breast enlargement in men
- flu-like symptoms, muscle weakness
- trembling
- decreased sharpness of vision
- severe headache often accompanied by nausea, vomiting and sensitivity to light
- oral or vaginal thrush
- pain or discomfort in the side of the body
- muscle and joint stiffness
- unconsciousness
- weight gain, feeling cold

If any of these affects you severely, tell your doctor.

The following other side effects have been reported in very few patients treated with Tasigna:
- confusion, disorientation
- sensation of numbness or tingling in fingers and toes
- reddening and/or swelling and possibly peeling on the palms and soles (so called hand-foot syndrome)
- increased sensitivity of the eyes or the skin to light
- eye pain or redness, pain, swelling and itching of the eyelids
- difficulty hearing, ear pain, noises (ringing) in the ears
- blood in urine, urinary incontinence

If any of these affects you severely, tell your doctor.

During Tasigna treatment, you may also have some abnormal blood test results such as low level of blood cells (white cells, red cells, platelets), high blood level of lipase or amylase (pancreas function), high blood level of bilirubin (liver function) or high blood level of creatinine (kidney function).

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE TASIGNA

- Keep out of the reach and sight of children.
- Do not use Tasigna after the expiry date which is stated on the carton and blister foil. The expiry date refers to the last day of that month.
- Do not store above 30°C.
- Store in the original package in order to protect from moisture.
- Do not use any pack that is damaged or shows signs of tampering.

6. FURTHER INFORMATION

What Tasigna contains
- The active substance is nilotinib. Each capsule contains 200 mg nilotinib (as hydrochloride monohydrate).
- The other ingredients are lactose monohydrate, crospovidone, poloxamer 188, silica colloidal anhydrous, magnesium stearate. The capsule shell is composed of gelatin, titanium dioxide (E171), yellow iron oxide (E172) and, shellac, red iron oxide (E172) and soya lecithin (E322) for stamping of the imprint.

What Tasigna looks like and contents of the pack
Tasigna is supplied as hard capsules. The capsules are light yellow. A red imprint is stamped on each capsule ("NVR/TKI").

Tasigna is available in weekly and monthly packs:
- The weekly pack contains 28 capsules.
- The monthly pack contains 112 capsules (4x28). A monthly pack consists of 4 individual weekly packs.

Not all packs may be marketed in your country.

Marketing Authorisation Holder
Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

Manufacturer
Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

Luxembourg/Luxemburg
Novartis Pharma GmbH
Tél/Tel: +49 911 273 0

България
Novartis Pharma Services Inc.
Тел.: +359 2 489 98 28

Česká republika
Novartis s.r.o.
Tel: +420 225 775 111

Danmark
Novartis Healthcare A/S
Tlf: +45 39 16 84 00

Deutschland
Novartis Pharma GmbH
Tel: +49 911 273 0

Eesti
Novartis Pharma Services Inc.
Tel: +372 66 30 810

Ελλάδα
Novartis (Hellas) A.E.B.E.
Τηλ: +30 210 281 17 12

España
Novartis Farmacéutica, S.A.
Tel: +34 93 306 42 00

France
Novartis Pharma S.A.S.
Tél: +33 1 55 47 66 00

Ireland
Novartis Ireland Limited
Tel: +353 1 260 12 55

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Novartis Farma S.p.A.
Tel: +39 02 96 54 1

Κύπρος
Novartis Pharma Services Inc.
Τηλ: +357 22 690 690

Latvija
Novartis Pharma Services Inc.
Tel: +371 67 887 070

Magyarország
Novartis Hungária Kft. Pharma
Tel.: +36 1 457 65 00

Malta
Novartis Pharma Services Inc.
Tel: +356 2298 3217

Nederland
Novartis Pharma B.V.
Tel: +31 26 37 82 111

Norge
Novartis Norge AS
Tlf: +47 23 05 20 00

Österreich
Novartis Pharma GmbH
Tel: +43 1 86 6570

Polska
Novartis Poland Sp. z o.o.
Tel.: +48 22 550 8888

Portugal
Novartis Farma - Produtos Farmacêuticos, S.A.
Tel: +351 21 000 8600

România
Novartis Pharma Services Inc.
Tel: +40 21 31299 01

Slovenija
Novartis Pharma Services Inc.
Tel: +386 1 300 75 50

Slovenská republika
Novartis Slovakia s.r.o.
Tel: +421 2 5542 5439

Suomi/Finland
Novartis Finland Oy
Puh/Tel: +358 (0)10 6133 200

Sverige
Novartis Sverige AB
Tel: +46 8 732 32 00

United Kingdom
Novartis Pharmaceuticals UK Ltd.
Tel: +44 1276 698370

Lietuva
Novartis Pharma Services Inc.
Tel: +370 5 269 16 50

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