SCHEDULING STATUS S4

PROPRIETARY NAME AND DOSAGE FORM

TASIGNA® 200 mg capsule

TASIGNA® 150 mg capsule

COMPOSITION

TASIGNA® 200 mg capsule:

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

List of excipients:

Capsule content: Lactose monohydrate; crospovidone; poloxamer 188; colloidal silicon dioxide; magnesium stearate

Capsule shell: Gelatin; titanium dioxide Iron oxide, yellow

Printing ink: Iron oxide, red

TASIGNA® 150 mg capsule:

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

List of excipients:

Capsule content: Lactose monohydrate; crospovidone; poloxamer 188; colloidal silicon dioxide; magnesium stearate

Capsule shell: Gelatin; titanium dioxide; iron oxide, yellow , iron oxide, red

Printing ink: Iron oxide, black

PHARMACOLOGICAL CLASSIFICATION

A.26 Cytostatic agents

PHARMACOLOGICAL ACTION

Pharmacodynamic properties:

Nilotinib is a potent and selective inhibitor of the Abl tyrosine kinase activity of the Bcr-Abl oncoprotein both in cell lines and in primary Philadelphia-chromosome positive leukaemia cells. Nilotinib binds with high affinity to the ATP-binding site in such a manner that it is a potent inhibitor of wild-type Bcr-Abl. 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.

Pharmacokinetic properties:

Absorption:

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

Administration of nilotinib 30 minutes or 2 hours after food increased bioavailability of nilotinib by 29% or 15 %, respectively (see **Dosage and Directions for use**, **Special precautions and Interactions**).

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

Distribution:

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

Biotransformation:

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

Elimination:

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

Linearity / non-linearity:

Steady-state nilotinib exposure was dose-dependent with less than dose-proportional increases in systemic exposure at dose levels higher than 400 mg given as once daily dosing. Daily serum exposure to nilotinib of 400 mg twice-daily dosing at steady state was 35 % higher than with 800 mg once-daily dosing. Systemic exposure (AUC) of nilotinib at steady state at a dose level of 400 mg twice daily was approximately 13,4 % higher than with 300 mg twice daily. The average nilotinib trough and peak concentrations over 12 months were approximately 15,7 % and 14,8 % higher following 400 mg twice daily dosing compared to 300 mg twice daily. There was no relevant

increase in exposure to nilotinib when the dose was increased from 400 mg twice-daily to 600 mg twice-daily.

Characteristics in patients:

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

INDICATIONS

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

CONTRA-INDICATIONS

Known hypersensitivity to nilotinib or to any of the excipients.

WARNINGS

QT Prolongation: TASIGNA prolongs the QT interval. Correct hypokalaemia or hypomagnesaemia prior to administration and monitor periodically. Avoid medicines known to prolong the QT interval and strong CYP3A4 inhibitors. Use caution in patients with hepatic impairment. Obtain ECGs at baseline, seven days after initiation, and periodically thereafter, as well as following any dose adjustments.
Sudden deaths: There were sudden deaths reported in the safety population and the expanded access program. Ventricular repolarization abnormalities may have contributed to their occurrence. Based on post-marketing exposure in patient-years, the estimated reporting rate for spontaneous reports of sudden death is 0.02 % per patient-year.

- Myelosuppression: Associated with neutropenia, thrombocytopenia and anaemia. A complete blood count (CBC**)** should be done every 2 weeks for the first 2 months, then monthly. Reversible by withholding dose. Dose reduction may be required.
- Elevated serum lipase: Caution is recommended in patients with history of pancreatitis. Check serum lipase periodically.
- Liver function abnormality: TASIGNA may result in elevations in bilirubin, AST/ALT, and alkaline phosphatase. Check hepatic function tests periodically.

- Electrolyte abnormalities: TASIGNA can cause hypophosphataemia, hypokalaemia, hyperkalaemia, hypocalcaemia, and hyponatraemia. Correct electrolyte abnormalities prior to initiating TASIGNA and monitor periodically during therapy.
- Hepatic impairment: TASIGNA has not been investigated in patients with hepatic impairment. Caution is recommended in these patients and QT interval should be monitored closely.
- Interactions: Avoid concomitant use of strong inhibitors or inducers of CYP3A4. If patients must be co-administered a strong CYP3A4 inhibitor, dose reduction should be considered and the QT interval should be monitored closely.
- Food Effects: Food increases blood levels of TASIGNA. Avoid food 2 hours before and 1 hour after a dose.
- Pregnancy: Fetal harm can occur when administered to a pregnant woman. Women should be advised not to become pregnant when taking TASIGNA.

INTERACTIONS

Medicines that inhibit or Induce cytochrome P450 3A4 enzymes:

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

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

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

Medicines that may increase nilotinib serum concentrations:

Nilotinib is mainly metabolised in the liver, and is also a substrate for the multi- medicine efflux pump, P-glycoprotein (Pgp). Therefore, absorption and subsequent elimination of systemically absorbed nilotinib may be influenced by medicines that affect CYP3A4 and/or Pgp. The bioavailability of nilotinib in healthy subjects was increased by 3-fold when co-administered with the strong CYP3A4 inhibitor ketoconazole. Concurrent treatment with strong CYP3A4 inhibitors should therefore be avoided. (including but not limited to ketoconazole, itraconazole, voriconazole, ritonavir, clarithromycin and telithromycin) (see **Dosage and directions for use and Special precautions** *regarding QT prolongation*). Alternative concomitant medications with no or minimal CYP3A4 inhibition should be considered.

Antidysrhythmic medicines and other medicines that may prolong QT:

TASIGNA should be used with caution in patients who have or may develop prolongation of QT including those patients taking anti-dysrhythmic medicines such as amiodarone, disopyramide, procainamide, quinidine and sotalol or other medicines that may lead to QT prolongation such as chloroquine, halofantrine, clarithromycin, haloperidol and methadone. (See **Special precautions***)*

Medicines that may decrease nilotinib serum concentrations:

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

Nilotinib has pH-dependent solubility, with lower solubility at higher pH. In healthy subjects receiving esomeprazole at 40 mg once daily for 5 days, gastric pH was markedly increased, but nilotinib absorption was only decreased modestly (27 % decrease in C_{max} and 34 % decrease in $AUC_{0-\infty}$). TASIGNA may be used concurrently with esomeprazole or other proton pump inhibitors as needed.

Medicines that may have their serum concentration altered by nilotinib:

Nilotinib is identified as a competitive inhibitor of CYP3A4, CYP2C8, CYP2C9, and CYP2D6 *in vitro*, with Ki value being lowest for CYP2C9 (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.

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 **Dosage and directions for use, Special precautions** and ***Pharmacokinetic properties***).

TASIGNA should not be taken in conjunction with food and should be taken at least 2 hours after a meal. No food should be consumed for at least one hour after the dose is taken. Grapefruit juice and other foods that are known to inhibit CYP3A4 should be avoided.

PREGNANCY AND LACTATION

Safety and efficacy in pregnancy and lactation has not been established.

Pregnancy:

There are no adequate data on the use of TASIGNA in pregnant women. Studies in animals showed no teratogenicity, but embryo- and fetotoxicity was seen at doses which also showed maternal toxicity. TASIGNA should not be used during pregnancy.

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.

Fertility:

No effects on sperm count/motility and on fertility were noted in male and female rats up to the highest tested dose approximately 5 times the recommended dosage for human. Sexually active male or female patients taking TASIGNA should use adequate contraception.

DOSAGE AND DIRECTIONS FOR USE

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

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

Dosing in patients with newly diagnosed Ph+ CML-Chronic Phase:

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

Dosing in patients with Ph+ CML-Chronic Phase and CML-Accelerated Phase resistant to or intolerant to at least one prior therapy including imatinib:

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

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

• Newly diagnosed CML in chronic phase at 300 mg twice daily • Chronic phase or Accelerated phase CML at 400 mg twice daily	(ANC) < 0,5 x 10^9/l 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 > 0,5 x 10^9/l and/or platelets > 50 x 10^9/l 3. If blood counts remain low a medicine reduction may be required to 400 mg once daily

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

Asymptomatic serum lipase elevations were observed. Few of these elevations were associated with clinical symptoms such as abdominal pain or a diagnosis of pancreatitis. Elevations in serum lipase did not lead to treatment discontinuation in any patient. Overall, this finding was clinically manageable in the majority of patients without requirement for dose reduction or interruption. For Grade 3 to 4 lipase elevations, doses were reduced to 400 mg once daily. (see **Side effects**).

In clinical studies, the majority of bilirubin and hepatic transaminase laboratory abnormalities in patients were of low grade toxicity which did not require dose interruption or reduction. Treatment discontinuation due to elevated serum bilirubin occurred in only 1 patient (0,3 %). For Grade 3 to 4 bilirubin or hepatic transaminase elevations, doses were reduced to 400 mg once daily. (see *Side-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. TASIGNA should not be used in these categories of patients.

Elderly patients:

Approximately 12 % and 30 % of subjects in clinical studies (newly diagnosed Ph+ CML-CP and resistant or intolerant Ph+ CML-Chronic Phase and CML-Accelerated Phase) were 65 or over. No major differences were observed for safety and efficacy in patients ≥ 65 years of age as compared to adults 18 to 65 years of age.

Patients with renal impairment:

Clinical studies have not been performed in patients with impaired renal function. Clinical studies 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:

TASIGNA has not been investigated in patients with hepatic impairment. Clinical studies have excluded patients with ALT and/ or AST > 2,5 (or > 5, if related to disease) times the upper limit of the normal range and/ or total bilirubin > 1,5 times the upper limit of the normal range. Metabolism of nilotinib is mainly hepatic.

Cardiac disorders:

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

SIDE EFFECTS AND SPECIAL PRECAUTIONS

Side effects:

Newly diagnosed Ph+ CML-Chronic Phase:

The data reported below reflect exposure to TASIGNA from a randomised 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, 64 months.

The very common non-haematologic adverse drug reactions (ADR's) 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 and asthenia were observed commonly (≤ 10 % and

> 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 the mean time-averaged QTcF increase at steady state were 6 msec. No patient had an absolute QTcF of > 500 msec in any of the treatment groups and no events of Torsade de Pointes were observed. QTcF increases from baseline that exceed 60 msec were observed in 3 patients (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.

Haematologic ADR's include myelosuppression: thrombocytopenia (17 %), neutropenia (15 %), and anaemia (7 %). See Table 3 for grade 3/4 laboratory abnormalities.

Discontinuation for 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 multicentre study treated at the recommended dose of 400 mg twice daily.

The most frequent (greater than 10 % in the combined CML-CP and CML-AP patient populations) non-haematologic adverse drug reactions (ADR's) were rash, pruritus, nausea, fatigue, headache, constipation, and diarrhoea. Most of these ADR's were mild to moderate in severity. Vomiting, myalgia, alopecia, muscle spasms, anorexia, arthralgia, bone pain, abdominal pain, peripheral oedema and asthenia were observed less frequently (< 10 % and > 5 %) and have been of mild to moderate severity (Grade 1 or 2). Discontinuation for adverse events regardless of causality was observed in 16 % of CP and 10 % of AP patients.

Pleural and pericardial effusions as well as complications of fluid retention occurred in 1 % of patients receiving TASIGNA. Congestive heart failure was observed in 1 % of patients. Gastrointestinal and CNS haemorrhage were reported in 3 % and 1 % of patients, respectively.

Sudden deaths and QT prolongation were reported. QTcF exceeding 500 msec was observed in < 1 % of patients.

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

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

Skin and subcutaneous tissue disorders: rash, pruritis
Gastrointestinal disorders: nausea, diarrhea, constipation, vomiting, abdominal pain
Nervous system disorders: headache
General disorders and administration site conditions: fatigue, pyrexia, asthenia, peripheral oedema
Musculoskeletal and connective tissue disorders: arthralgia, myalgia, pain in extremity, bone pain, muscle spasms, back pain
Respiratory, thoracic and mediastinal disorders: cough, dyspnoea
Infections and infestations: nasopharyngitis

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

		CML-CP N=318		CML-AP N=120	
Body System and Preferred Term		**All Grades (%)**	**CTC Grades[b] 3/4 (%)**	**All Grades (%)**	**CTC Grades[b] 3/4 (%)**
Skin and subcutaneous tissue disorders	Rash	33	2	28	0
	Pruritus	29	1	20	0
Gastrointestinal disorders	Nausea	31	1	18	<1
	Diarrhoea	22	3	19	2
	Constipation	21	<1	18	0
	Vomiting	21	<1	10	0
	Abdominal pain	11	1	13	3
Nervous system disorders	Headache	31	3	21	2
General disorders and administration site conditions	Fatigue	28	1	16	<1
	Pyrexia	14	1	24	2
	Asthenia	14	0	12	2
	Oedema, peripheral	11	0	11	0
Musculoskeletal and connective tissue disorders	Arthralgia	18	2	16	0
	Myalgia	14	2	14	<1
	Pain in extremity	13	1	16	2
	Bone pain	11	<1	13	<1
	Muscle spasms	11	<1	14	0
	Back pain	10	<1	12	<1
Respiratory, thoracic and mediastinal disorders	Cough	17	<1		13
	Dyspn**o**ea	11	1		8
Infections and infestations	Nasopharyngitis	16	<1		11

[a] Excluding laboratory abnormalities

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

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

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

	Newly diagnosed Ph+ CML-CP		Resistant or intolerant Ph+	
	TASIGNA 300 mg bd N=279	**TASIGNA 400 mg bd N=277**	**CML-CP N=321**	**CML-AP N=137**
Haematologic Parameters				
Myelosuppression				
Thrombocytopenia	10 %[1]	12 %[1]	30 %[1]	42 %[2]
Neutropenia[2]	12 %	10 %	31 %	42 %[3]
Anaemia	4 %	4 %	11 %	27 %
Biochemistry Parameters				
Elevated lipase	7 %	7 %	18 %	18 %
Hypophosphataemia	5 %	6 %	17 %	15 %
Elevated bilirubin (total)	4%	8 %	7 %	9 %
Elevated ALT	4 %	9 %	4 %	4 %
Elevated AST	1 %	3 %	3 %	2 %
Elevated creatinine	0 %	0 %	1 %	< 1 %

* NCI Common Terminology Criteria for Adverse Events, version 3.0

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

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

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

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 ≥ 5 %**.** The corresponding frequency category using the following convention (CIOMS III) is provided for each adverse reaction: (common is ≥ 1/100 and < 1/10; uncommon is ≥ 1/1,000 and < 1/100; single events are captured as unknown in frequency). For laboratory abnormalities, very common events (≥ 1/10) not included in Table 3 are also reported. These adverse reactions are included based on clinical relevance and are listed according to MedDRA system organ class. The adverse reactions are ranked in decreasing order of frequency within each category.

Infections and infestations:

Common: folliculitis

Uncommon: pneumonia, urinary tract infection, gastroenteritis, upper respiratory tract infection (including pharyngitis, nasopharyngitis, rhinitis).

Unknown frequency: sepsis, bronchitis, herpes virus infection, candidiasis, subcutaneous abcess, anal abcess, furuncle, tinea pedis.

Neoplasms Benign, Malignant and Unspecified:

Common: skin papilloma

Unknown frequency: papilloma.

Blood and lymphatic system disorders*:*

Common: febrile neutropenia, pancytopenia, lymphopenia.

Unknown frequency: thrombocythaemia, leukocytosis.

Immune system disorders:

Unknown frequency: hypersensitivity.

Endocrine disorders:

Uncommon: hyperthyroidism, hypothyroidism.

Unknown frequency: thyroiditis, secondary hyperparathyroidism

Metabolism and nutrition disorders*:*

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

Uncommon: dehydration, decreased appetite, increased appetite.

Unknown frequency: hyperuricaemia, gout, hypoglycaemia, dyslipidaemia.

Psychiatric disorders*:*

Common: depression, insomnia.

Uncommon: anxiety.

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

Nervous system disorders*:*

Common: dizziness, paraesthesia, hypoaesthesia.

Uncommon: intracranial haemorrhage, loss of consciousness (including syncope), migraine, tremor, disturbance in attention, hyperaesthesia.

Unknown frequency: brain oedema, peripheral neuropathy, optic neuritis, lethargy, dysaesthesia.

Eye disorders*:*

Common: eye haemorrhage, periorbital oedema, eye pruritus, conjunctivitis, dry eye.

Uncommon: vision impairment, blurred vision, visual acuity reduced, eye irritation, eyelid oedema, photopsia.

Unknown frequency: papilloedema, diplopia, eye swelling, photophobia, blepharitis, eye pain, chorioretinopathy, conjunctival haemorrhage, allergic conjunctivitis, conjunctival hyperaemia, ocular hyperaemia, ocular surface disease, scleral hyperaemia.

Ear and labyrinth disorders*:*

Common: vertigo.

Unknown frequency: hearing impaired, ear pain, tinnitus.

Cardiac disorders:

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

Uncommon: cardiac failure, pericardial effusion, coronary artery disease, cardiac murmur, cyanosis.

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

Vascular disorders:

Common: flushing, hypertension.

Uncommon: hypertensive crisis, haematoma.

Unknown frequency: shock haemorrhagic, hypotension, thrombosis.

Respiratory, thoracic and mediastinal disorders:

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

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

Unknown frequency: pulmonary hypertension, wheezing.

Gastrointestinal disorders:

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

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

Unknown frequency: gastric ulcer, gastrointestinal ulcer perforation, retroperitoneal haemorrhage, haematemesis, ulcerative oesophagitis, subileus, gastritis, haemorrhoids, hiatus hernia, rectal haemorrhage, sensitivity of teeth, gingivitis.

Hepatobiliary disorders:

Common: abnormal hepatic function.

Uncommon: hepatitis, jaundice.

Unknown frequency: cholestasis, hepatotoxicity, hepatomegaly.

Skin and subcutaneous tissue disorders:

Common: dry skin, night sweats, erythema, hyperhidrosis, contusion, acne, dermatitis, eczema, urticaria.

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

Unknown frequency: erythema nodosum, skin ulcer, palmar-plantar erythrodysaesthesia syndrome, petechiae, photosensitivity, blister, dermal cyst, sebaceous hyperplasia, skin atrophy, skin discolouration, skin exfoliation, skin hyperpigmentation, skin hypertrophy.

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, erectile dysfunction, gynaecomastia.

Unknown frequency: breast induration, menorrhagia, nipple swelling.

General disorders and administration site conditions:

Common: chest pain, pain (including neck pain and back pain), pyrexia, chest discomfort.

Uncommon: face oedema, gravitational oedema, influenza-like illness, chills, malaise.

Unknown frequency: feeling hot, localised oedema.

Investigations:

Common: increased blood amylase, decreased weight , increased gamma-glutamyltransferase, increased weight, increased blood creatinine phosphokinase.

Uncommon: increased blood lactate dehydrogenase, increased blood urea, decreased haemoglobin.

Unknown frequency: increased troponin, increased blood bilirubin unconjugated, blood insulin, increased very low density lipoprotein, increased blood parathyroid hormone, increased blood pressure.

Special precautions:

Myelosuppression:

Treatment with TASIGNA is associated with thrombocytopenia, neutropenia and anaemia (NCI CTC Grade 3/4). The occurrence is more frequent in patients with imatinib-resistant or intolerant CML and, in particular in patients with 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 directions for use**).

QT prolongation:

In vitro data suggest that TASIGNA has the potential to prolong cardiac ventricular repolarisation (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 6 and 8 msec, respectively. QTcF of > 500 msec was observed in < 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 dysrhythmias were observed during the conduct of the trial. In particular, no episodes of torsade de pointes (either transient or sustained) were observed (see **Warnings**).

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

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.

Total gastrectomy:

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

Medicine interactions:

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 **Interactions**). If transient interruption of treatment with TASIGNA is not possible, close monitoring of the individual for prolongation of the QT interval is indicated (see **Dosage and directions for use**, **Interactions** and **Pharmacokinetic properties**).

Food effect:

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

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

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

Hepatic impairment:

TASIGNA has not been investigated in patients with hepatic impairment. Clinical studies have excluded patients with ALT and/ or AST > 2,5 (or > 5, if related to disease) times the upper limit of the normal range and/ or total bilirubin > 1,5 times the upper limit of the normal range. Metabolism of nilotinib is mainly hepatic. Caution is recommended in patients with hepatic impairment (see **Dosage and directions for use**).

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.

Effects on ability to drive and use machines:

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Isolated reports on 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.

IDENTIFICATION

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

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

PRESENTATION

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

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

Not all pack sizes may be marketed.

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

STORAGE INSTRUCTIONS

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

Keep out of the reach of children.

REGISTRATION NUMBER

TASIGNA® 200 mg capsule: 41/26/0973

TASIGNA® 150 mg capsule: 45/26/0410

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

NOVARTIS SOUTH AFRICA (PTY) LTD

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