Tasigna®
(nilotinib)

A Guide to the Dosing and Administration of TASIGNA

Introduction

This guide to the dosing and administration of TASIGNA has been developed as part of a plan to help reduce the risk of serious adverse reactions and maximize the benefit-risk profile of TASIGNA. The purpose of this brochure is to ensure that health care professionals prescribing TASIGNA

- Understand specific drug-drug interactions, drug-food interactions, and risks associated with comorbidities
- Conduct appropriate electrocardiogram (ECG) and electrolyte monitoring for patients taking TASIGNA
- Advise patients on the proper dosing of TASIGNA and the need to take TASIGNA in a fasting state

Indications[1]

- TASIGNA (nilotinib) is indicated for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in the chronic phase (CP)
- TASIGNA is indicated for the treatment of CP and accelerated phase (AP) Ph+ CML in adult patients resistant or intolerant to prior therapy, including imatinib

TASIGNA efficacy in clinical trials[1]

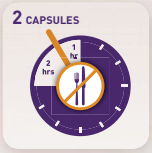
- **In newly diagnosed patients with Ph+ CML-CP**
  - TASIGNA achieved statistically superior rates of **major molecular response** (MMR) compared with imatinib at 12 months (44% vs 22%; *P*<0.0001), the primary endpoint of the trial
  - TASIGNA showed a statistically significant improvement in time to **progression to AP or blast crisis** compared with imatinib (*P*=0.0059): at 60 months, 99.3% of patients on core treatment taking TASIGNA vs 95.2% of patients taking imatinib remained progression free
  - TASIGNA achieved significantly higher MMR rates compared with imatinib by 60 months (77% vs 60%; *P*<0.0001)
- **In imatinib-resistant or -intolerant patients with Ph+ CML-CP**
  - The primary endpoint of the trial was major cytogenetic response (MCyR); 51% achieved MCyR
  - TASIGNA demonstrates a high survival rate, with 87% **overall survival** at 24 months
  - TASIGNA delivers **powerful, durable responses,** with 37% of patients achieving **complete cytogenetic response** (CCyR) at the time of the 2-year analysis, and 85% maintaining CCyR for at least 24 months

How to Dose TASIGNA

Dosing and administration[1]

- **The recommended dose of TASIGNA for Ph+ CML is:**
  - 300 mg (2 x 150-mg capsules) twice daily for newly diagnosed adult patients in CP
  - 400 mg (2 x 200-mg capsules) twice daily for imatinib-resistant or -intolerant adult patients in CP or AP
- TASIGNA is available in 2 capsule strengths: 150 mg and 200 mg

- **TASIGNA should be dosed twice daily.** Each capsule should be swallowed whole with water; doses should be administered approximately 12 hours apart
  - For example, 2 capsules in the morning and 2 capsules in the evening



- **TASIGNA must not be taken with food**
  - Patients should not eat for 2 hours before and at least 1 hour after taking TASIGNA
  - If a dose is missed, patients should not make up the dose, but take the next dose as scheduled
  - For patients who are unable to swallow capsules, the contents of each capsule may be dispersed in 1 teaspoon of applesauce (puréed apple) and should be taken immediately. Not more than 1 teaspoon of applesauce and no food other than applesauce may be used
- Your Novartis Sales Specialist may provide you with tools to help you educate your patients about the dosing schedule of TASIGNA
- **TASIGNA should NOT be taken at any time with grapefruit juice** or other foods that are known to inhibit CYP3A4. These foods should be avoided while taking TASIGNA

Dosing adjustments and modifications[1]

- TASIGNA may need to be temporarily withheld and/or dose reduced for hematologic toxicities (neutropenia, thrombocytopenia) that are not related to underlying leukemia

Dose adjustments for neutropenia and thrombocytopenia

Newly diagnosed Ph+ CML-CP at 300 mg bid or imatinib-resistant or -intolerant Ph+ CML-CP at 400 mg bid	**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.
Imatinib-resistant or -intolerant Ph+ CML-AP at 400 mg bid	**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.

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- If clinically significant, moderate, or severe nonhematologic toxicity develops, dosing should be interrupted, and may be resumed at 400 mg once daily after the toxicity has resolved. If clinically appropriate, re-escalation of the dose to the starting dose of 300 mg twice daily in newly diagnosed patients with Ph+ CML-CP or to 400 mg twice daily in patients with imatinib-resistant or -intolerant Ph+ CML-CP or -AP should be considered
- For Grade 3 or 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
- For Grade 3 or 4 bilirubin or hepatic transaminase elevations, doses should be reduced to 400 mg once daily or interrupted. Bilirubin and hepatic transaminase levels should be tested monthly or as clinically indicated

Important considerations[1]

Antiarrhythmic medicines and other drugs that may prolong the QT interval should be used with caution

- Concomitant use of antiarrhythmic medicines (including, but not limited to, amiodarone, disopyramide, procainamide, quinidine, and sotalol) and other drugs that may prolong the QT interval (including, but not limited to, chloroquine, halofantrine, clarithromycin, haloperidol, methadone, and moxifloxacin) should be used with caution
- Should treatment with any of these agents be required, it is recommended that therapy with TASIGNA be interrupted if possible. If transient interruption of treatment with TASIGNA is not possible, close monitoring of the individual for prolongation of the QT interval is indicated

Patients should not take TASIGNA with food

- The bioavailability of TASIGNA is increased with food
- Patients should not eat for 2 hours before and at least 1 hour after taking TASIGNA
- Foods that are known to inhibit CYP3A4, such as grapefruit juice, should be avoided during therapy

TASIGNA is primarily metabolized by CYP3A4
Concomitant strong CYP3A4 inhibitors should be avoided with TASIGNA

- The concomitant use of strong CYP3A4 inhibitors (including, but not limited to, ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, and ritonavir) should be avoided
- Should treatment with any of these agents be required, it is recommended that therapy with TASIGNA be interrupted if possible. If transient interruption of treatment with TASIGNA is not possible, close monitoring of the individual for prolongation of the QT interval is indicated
- Foods that are known to inhibit CYP3A4, such as grapefruit juice, may also increase serum concentrations of TASIGNA and should be avoided

Concomitant strong CYP3A4 inducers should be avoided with TASIGNA

- The concomitant use of strong CYP3A4 inducers (eg, phenytoin, rifampicin, carbamazepine, phenobarbital, and St. John's wort) should be avoided
- In patients for who CYP3A4 inducers are indicated, alternative agents with less enzyme-induction potential should be considered
- **Substances that may have their systemic concentration altered by nilotinib**
  - Nilotinib is a moderate CYP3A4 inhibitor. As a result, the systemic exposure of other drugs primarily metabolized by CYP3A4 (eg, certain HMG-CoA reductase inhibitors) may be increased when co-administered with nilotinib. Appropriate monitoring and dose adjustment may be necessary for drugs that are CYP3A4 substrates and have a narrow therapeutic index (including, but not limited to, alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, sirolimus, and tacrolimus) when co-administered with nilotinib

Cardiovascular events

- Cardiovascular events, including peripheral arterial occlusive disease, ischemic heart disease, and ischemic cerebrovascular events, have been reported in patients taking TASIGNA. Patients should be advised to seek immediate medical attention if they experience acute signs or symptoms of cardiovascular events. The cardiovascular status of patients should be evaluated and cardiovascular risk factors should be monitored and actively managed during TASIGNA therapy according to standard guidelines. Appropriate therapy should be prescribed to manage cardiovascular risk factors

Caution is recommended in patients with certain pre-existing conditions

- Use with caution in patients with a history of uncontrolled or significant cardiac disease
  - In clinical studies, patients with uncontrolled or significant cardiac disease, including recent myocardial infarction, congestive heart failure, unstable angina, or clinically significant bradycardia, were excluded
- Use with caution in patients with hepatic impairment. Hepatic impairment has a modest effect on the pharmacokinetics of TASIGNA. Dose adjustment is not considered necessary in hepatically impaired patients, but patients with hepatic impairment should be treated with caution
- Use with caution in patients with a history of pancreatitis. Elevations of lipase and amylase have been observed in patients taking TASIGNA

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Lactose

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

Periodic monitoring is recommended with TASIGNA

- For electrolyte abnormalities, such as hypokalemia or hypomagnesemia
- For QT prolongation, ECGs should be obtained to monitor the QTc at baseline and as clinically indicated
- For laboratory abnormalities, such as hypercholesterolemia and hyperglycemia, cholesterol and blood glucose levels should be monitored at baseline and as clinically indicated

Tumor lysis syndrome

- Cases of tumor lysis syndrome have been reported in patients treated with TASIGNA. Correction of clinically significant dehydration and treatment of high uric acid levels are recommended prior to initiating TASIGNA therapy

Other important information

- Fluid retention, cardiac failure, and pulmonary edema have been reported with TASIGNA. Patients should be monitored
- Severe forms of fluid retention, such as pleural effusion, pulmonary edema, and pericardial effusion, were uncommonly (0.1% to 1%) observed in a Phase III study of newly diagnosed CML patients. Similar events were observed in post-marketing reports. Unexpected, rapid weight gain should be carefully investigated. If signs of severe fluid retention appear during treatment with TASIGNA, the etiology should be evaluated and patients treated accordingly
- Lipid profiles should be determined prior to initiating TASIGNA therapy, assessed at month 3 and 6 after initiating therapy, and at least yearly during chronic therapy
- Increases in blood glucose levels have been reported with TASIGNA therapy. Blood glucose levels should be assessed prior to initiating TASIGNA therapy and monitored during treatment

TASIGNA and Special Populations[1]

Children and adolescents

- TASIGNA is not recommended for use in children and adolescents under 18 years of age, as the safety and efficacy have not been established in this age group

Elderly patients

- Approximately 12% of subjects in the Phase III study of TASIGNA in patients with newly diagnosed Ph+ CML-CP and approximately 30% of subjects in the Phase II study in patients with imatinib-resistant or -intolerant Ph+ CML-CP or -AP were 65 years of age or older. No major differences were observed for safety and efficacy in patients ≥65 years of age compared with adults aged 18 to 65 years

Renal impairment

- TASIGNA has not been investigated in patients with impaired renal function. As TASIGNA and its metabolites are not renally excreted, a decrease in total body clearance is not expected in patients with renal impairment

Pregnancy

- There are no adequate data from the use of TASIGNA in pregnant women. Studies in animals have shown no teratogenicity, but embryotoxicity and fetotoxicity were observed at doses that showed maternal toxicity. TASIGNA should not be used during pregnancy unless absolutely necessary. If TASIGNA is given during pregnancy, the patient must be informed of the potential risk to the fetus
- Women of childbearing potential must be advised to use highly effective contraception during treatment with TASIGNA and for up to 2 weeks after ending treatment

Lactation

- Women should not breast-feed while taking TASIGNA, as a risk to the infant cannot be excluded

Important Information Regarding QT Prolongation[1]

- TASIGNA has been shown to prolong the QT interval in some patients
- In the Phase III study in patients with **newly diagnosed** Ph+ CML-CP receiving TASIGNA 300 mg twice daily, the change from baseline in mean time-averaged QTcF interval at steady state was 6 msec
  - No patient had a QTcF >480 msec
  - No episodes of torsades de pointes were observed
- In the Phase II study in **imatinib-resistant or -intolerant** Ph+ CML patients in CP or AP receiving 400 mg of TASIGNA twice daily, the change from baseline in mean time-averaged QTcF interval at steady state was 5 msec and 8 msec, respectively
  - QTcF of >500 msec was observed in <1% of these patients
  - No episodes of torsades de pointes were observed
- No cases of sudden death were reported in the Phase III study of TASIGNA in patients with **newly diagnosed** Ph+ CML-CP
- Uncommon cases (0.1% to 1%) of sudden death have been reported in **imatinib-resistant or -intolerant** Ph+ CML patients in CP or AP who received TASIGNA and who had a medical history of cardiac disease or significant cardiac risk factors
  - Comorbidities, in addition to the underlying malignancy, were also frequently present, as were concomitant medications. Ventricular repolarization abnormalities may have been contributory factors

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Managing Risk for QT Prolongation[1]

- **TASIGNA should be used with caution in patients with, or at significant risk of developing, QT prolongation**
- Close monitoring for an effect on the QT interval is advisable, with a baseline ECG recommended prior to initiating therapy with TASIGNA and as clinically indicated
- **Hypokalemia and hypomagnesemia must be corrected prior to TASIGNA administration, and blood levels should be periodically monitored**
- TASIGNA should be used with caution in patients taking drugs known to prolong the QT interval and should be avoided in patients taking strong CYP3A4 inhibitors
- Patients should avoid food 2 hours before and at least 1 hour after taking dose
- Use with caution in patients with congenital QT prolongation or uncontrolled or significant cardiac disease, including recent myocardial infarction, congestive heart failure, unstable angina, or clinically significant bradycardia
- Use with caution in patients with hepatic impairment

For more information about TASIGNA, speak to your local Novartis Representative or visit www.TASIGNA.com.

Any suspected adverse reactions and medication errors can be reported via the national Adverse Drug Reactions ADRs reporting system. Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to Medicines Authority Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gzira GZR 1368, MALTA, or sent by email to postlicensing.medicinesauthority@gov.mt

Healthcare professionals may also report any adverse events suspected to be associated with the use of Tasigna to Novartis Pharma Services Inc. Representative Office Malta by phone on 21222872, by fax on 22487219 or e-mail at drug_safety.malta@novartis.com

Reference: 1. Novartis Europharm Ltd. Tasigna Summary of Product Charecteristics.

NOVARTIS ONCOLOGY

Tasigna® (nilotinib)

TAS HCPG 04/15 MT

TASIGNA® 150mg Capsules

PRESENTATION: 150mg Capsules: White to yellowish powder in red opaque hard gelatin capsules, size 1 with black axial imprint "NVR/BCR". One hard capsule contains 150mg nilotinib.

INDICATIONS: TASIGNA is indicated for adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in the chronic phase.

DOSAGE AND ADMINISTRATION: Therapy should be initiated by a physician experienced in the treatment of patients with CML. The recommended dose of TASIGNA is 300mg twice daily. Treatment should be continued as long as the patient continues to benefit. For a dose of 400 mg once daily, 200mg capsules are available. Tasigna may need to be temporarily withheld and/or dose reduced for haematological toxicities (neutropenia, thrombocytopenia) that are not related to the underlying leukaemia. 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 2 hours before the dose is taken and no food should be consumed for at least one hour after the dose is taken. See the full SPC for full prescribing information for 150mg dose. If a dose is missed the patient should not take an additional dose, but take the usual prescribed next dose. Increases in serum cholesterol and blood glucose levels have been reported with Tasigna therapy. The safety and efficacy of Tasigna in children from birth to less than 18 years have not yet been established. Therefore, its use in paediatric patients is not recommended due to a lack of data on safety and efficacy.

CONTRAINDICATIONS: Known hypersensitivity to the nilotinib or to any of the excipients.

WARNINGS/PRECAUTIONS: Treatment with TASIGNA is associated with thrombocytopenia, neutropenia and anaemia (NCI CTC Grade 3/4). Occurrence is more frequent in patients with imatinib-resistant or intolerant CML, in particular 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. TASIGNA should be used with caution in patients who have or who are at significant risk of developing prolongation of the QT interval. These include patients with congenital long QT interval prolongation, with uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia. Close monitoring for an effect on the QT interval is advisable and a baseline ECG is recommended prior to initiating therapy with Tasigna. Hypokalaemia or hypomagnesaemia should be corrected prior to TASIGNA administration and monitored periodically during therapy. It is recommended that the glucose levels be assessed before initiating treatment with Tasigna and monitored during treatment, as clinically indicated (see section 4.2). If test results warrant therapy, physicians should follow their local standards of practice and treatment guidelines. Uncommon cases (0.1 to 1%) of sudden deaths have been reported in patients with imatinib-resistant or intolerant CML in chronic phase or accelerated phase 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 medicinal products. Ventricular repolarisation abnormalities may have been contributory factors. Severe forms of fluid retention such as pleural effusion, pulmonary oedema, and pericardial effusion were uncommonly (0.1 to 1%) observed in a Phase III study of newly diagnosed CML patients. Similar events were observed in post-marketing reports. Unexpected, rapid weight gain should be carefully investigated. If signs of severe fluid retention appear during treatment with nilotinib, the aetiology should be evaluated and patients treated accordingly. Cardiovascular events were reported in a randomised Phase III study in newly diagnosed CML patients and observed in post-marketing reports. Patients should be advised to seek immediate medical attention if they experience acute signs or symptoms of cardiovascular events. The cardiovascular status of patients should be evaluated and cardiovascular risk factors monitored and actively managed during Tasigna therapy according to standard guidelines. Appropriate therapy should be prescribed to manage cardiovascular risk factors.

INTERACTIONS: Tasigna may be given in combination with haematopoietic growth factors such as erythropoietin or granulocyte colony-stimulating factor (G-CSF) if clinically indicated. It may be given with hydroxyurea or anagrelide if clinically indicated. 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. If transient interruption of treatment is not possible, close monitoring of the individual for prolongation of the QT interval is indicated (see SPC for full prescribing information). ♦The concomitant administration of other medications that induce CYP3A4 (e.g. phenytoin, carbamazepine, phenobarbital, and St. John's Wort) may reduce exposure to nilotinib. Rifampicin (a potent CYP3A4 inducer) and nilotinib should not be used concomitantly. In patients for whom CYP3A4 inducers are indicated, alternative agents with less enzyme induction potential should be considered. Caution should be exercised when co-administering TASIGNA with substrates of these enzymes (CYP3A4, CYP2C8, CYP2C9, and CYP2D6) that have a narrow therapeutic index. In CML patients, nilotinib administered at 400 mg twice daily for 12 days increased the systemic exposure of oral midazolam (a substrate of CYP3A4). Nilotinib is a moderate CYP3A4 inhibitor. As a result, the systemic exposure of other drugs primarily metabolised by CYP3A4 (e.g. certain HMG-CoA reductase inhibitors) may be increased when co-administered with nilotinib. Tasigna may be used concurrently with esomeprazole or other proton pump inhibitors as needed. Caution is recommended in patients with previous history of pancreatitis. Grapefruit juice and other foods that are known to inhibit CYP3A4 should be avoided. TASIGNA is not recommended for patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

ADVERSE REACTIONS: The following adverse reactions (excluding laboratory abnormalities) were reported in at least 5% of the patients in TASIGNA clinical studies: Very common: Headache, Nausea, Alopecia, Constipation, Diarrhoea, Rash, Pruritus, Fatigue, Myalgia, Vomiting, Less Common: Decreased appetite**,** Abdominal pain, Upper Abdominal Pain, Alopecia, Arthralgia, Muscle spasms, Bone pain, Asthenia, Peripheral Oedema, Dry Skin, Erythema. The following adverse reactions were reported in patients in the TASIGNA clinical studies at a frequency of less than 5%: ♦ Very common: alanine aminotransferase increased, aspartate aminotransferase increased, lipase increased. hypophosphataemia, hyperbilirubinaemia (including blood bilirubin increased) ♦ Common: chest pain (including non-cardiac chest pain), pain, pyrexia, chest discomfort, malaise, disturbance in attention, neck pain, lipase increased, xerophthalmia, folliculitis, upper respiratory tract infection (including pharyngitis, nasopharyngitis, rhinitis) skin papilloma, febrile neutropenia, pancytopenia, eosinophilia, lymphopenia, electrolyte imbalance (including hypomagnasaemia, hyperkalaemia, hypokalaemia, hyponatraemia, hypocalcaemia, hypophosphataemia, hypercalcaemia, hyperphosphataemia,), diabetes mellitus, hyperglycaemia, hypercholesterolaemia, hyperlipidaemia, hypertriglyceridaemia, decreased appetite, depression, insomnia, anxiety, dizziness, peripheral neuropathy, hypoaesthesia, paraesthesia, eye haemorrhage, periorbital oedema, eye pruritus, conjunctivitis, dry eye, vertigo, angina pectoris, arrythmia (including atrioventricular block, cardiac flutter, extrasystoles, tachycardia, atrial fibrillation, bradycardia), palpitations, electrocardiogram QT prolonged, hypertension, flushing, dyspnoea, dyspnoea exertional, epistaxis, cough, dysphonia, pancreatitis, abdominal discomfort, abdominal distension, Dysgeusia, flatulence, hepatic function abnormal, night sweats, eczema, urticaria, erythema, hyperhidrosis, contusion, acne, dermatitis (including allergic and acneiform), dry skin, musculoskeletal chest pain, musculoskeletal pain, back pain, (flank pain), pollakiuria, chest pain (including non -cardiac chest pain), pain (including neck pain and back pain), pyrexia, chest discomfort, malaise, haemoglobin decreased, platelet count decreased blood amylase increased, blood alkaline phosphotase increased, gamma-glutamyltransferase increased, blood creatinine phosphokinase increased, blood insulin increased, lipoprotein increased (including very low density and high density), weight decreased, weight increased, ♦ Uncommon: intermittent claudication, arterial stenosis limb, face oedema, gravitational oedema, influenza-like illness, chills, feeling body temperature change (including feeling hot, feeling cold) muscoskeletal stiffness, breast pain, blood lactate dehydrogenase increased, blood glucose decreased, blood urea increased, globulins increased, gynaecomastia, erectile dysfunction, dysuria, micturition urgency, nocturia, muscular weakness, joint swelling, exfoliative rash, drug eruption, skin pain, ecchymosis, swelling face, hepatotoxicity, toxic hepatitis, jaundice, dry mouth, gastrointestinal haemorrhage, melaema, mouth ulceration, gastroesophageal reflux, stomatitis, oeophageal pain, pulmonary oedema, pleural effusion, interstitial lung disease, pleuritic pain, pleurisy, pharyngolaryngeal pain, throat irritation, haematoma, arteriosclerosis, hypertensive crisis, cardiac murmur, cyanosis, cardiac failure, pericardial effusion, coronary artery disease, hyperaesthesia, visual impairment, vision blurred, conjunctival haemorrhage, visual acuity reduced, eyelid oedema, photopsia, hyperaemia (scleral, conjunctival, ocular) eye irritation, tremor, loss of consciousness, (including syncope), migraine, intracranial haemorrhage, dyslipidaemia, increased apetite, dehydration, hyperthyroidism, hypothyroidism, thrombocythaemia, leukocytosis, pneumonia, urinary tract infection, gastroenteritis, bronchitis, herpes virus infection, candidiasis (including oral candidiasis) globulins decreased, sensitivity of teeth, gastritis, pleural effusion, peripheral arterial occlusive disease, gout, toxic hepatitis. ♦ Not known: Papilloedema, localized oedema, breast induration, menorrhagia, nipple swelling, cholestasis, renal failure, hematuria, urinary incontinence, chromaturia, troponin increased, blood bilirubin unconjugated increased, hepatomegaly, arthritis, gastrointestinal ulcer perforation, oesophagitis ulcerative, subileus, petechiae, photosensitivity, blister, dermal cysts, sebaceous hyperplasia, skin atrophy, skin discolouration, skin exfoliation, skin hyperpigmentation, skin hypertrophy, enterocolitis, haemorrhoids, hiatus hernia, rectal hemorrhage, gingivitis, retroperitoneal haemorrhage, haematemesis, gastric ulcer, pulmonary hypertension, wheezing, oropharyngeal pain, thrombosis, shock haemorrhagic, hypotension, ventricular dysfunction, erythema multiforme, erythema nodosum, skin ulcer, palmar-plantar erythrodysaesthesia syndrome, pericarditis, ejection fraction decreased, hearing impaired, ear pain, ocular surface disease, tinnitus, conjunctivitis allergic, blepharitis, eye pain, eye swelling, photophobia, chorioretinopathy, diplopia confusional state, amnesia, dysphoria, disorientation, hyperuricaemia, hypoglycaemia, hyperparathyroidism secondary, thyroiditis, hypersensitivity, oral papilloma, paraproteinaemia sepsis, subcutaneous abscess, anal abscess, furuncle, tinea pedis, transient ischaemic attack, blood parathyroid hormone

increased, brain oedema, optic neuritis, lethargy, dysaesthesia, restless legs syndrome, blood insulin decreased, insulin C-peptide decreased, paraproteinaemia, conjunctival haemorrhage, myocardial infarction, oropharyngeal pain, hyperkeratosis, psoriasis. Discontinuation due to adverse drug reactions was observed in 10% of patients.Please refer to the SPC for a full list of all adverse reactions reported.

LEGAL CATEGORY: POM.

MARKETING AUTHORISATION HOLDER: Novartis Europharm Limited, Frimley Business Park, Camberley, GU16 7SR, United Kingdom.

MARKETING AUTHORISATION NUMBER: EU/1/07/422/001 – 4.

Please refer to Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available on request from Novartis Pharma Services, P.O. Box 4, MRS 1000, Marsa, Malta. Tel +356 21222872.

2014-MT-TAS-15-DEC-2014

TASIGNA® (nilotinib) 200mg Capsules

PRESENTATION: 200mg Capsules: White to yellowish powder in light yellow opaque hard gelatin capsules, size 0 with red axial imprint "NVR/TKI"

INDICATIONS: TASIGNA is indicated for adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in the chronic phase. Chronic phase and accelerated phase Philadelphia chromosome positive CML with resistance or intolerant to prior therapy including imatinib. Efficacy data in patients with CML in blast crisis are not available.

DOSAGE AND ADMINISTRATION: Therapy should be initiated by a physician experienced in the treatment of patients with CML. The recommended dose of TASIGNA is 300mg twice daily in newly diagnosed patients with CML in the chronic phase. 400 mg twice daily in patients with chronic or accelerated phase CML with resistance or intolerance to prior therapy. Treatment should be continued as long as the patient continues to benefit. For a dose of 300mg twice daily, 150mg capsules are available. 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 2 hours before the dose is taken and no food should be consumed for at least one hour after the dose is taken. See the full SPC for full prescribing information for 150mg dose. If a dose is missed the patient should not take an additional dose, but take the usual prescribed next dose. Increases in serum cholesterol and blood glucose levels have been reported with Tasigna therapy. The safety and efficacy of Tasigna in children from birth to less than 18 years have not yet been established. Therefore, its use in paediatric patients is not recommended due to a lack of data on safety and efficacy.

DOSE ADJUSTMENTS: (See SPC for full prescribing information). **Haematological adverse reactions**: TASIGNA may need to be temporarily withheld and/or dose reduced for haematological toxicities (neutropenia, thrombocytopenia) that are not related to the underlying leukaemia. **Non-haematological adverse reactions:** 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. In case lipase elevations are accompanied by abdominal symptoms, Tasign should be interrupted and appropriate diagnostic measures considered to exclude pancreatitis. **Total Gastrectomy:** Nilotinib absorption (relative bioavailability) might be reduced by approximately 48% in patients with a total gastrectomy and 22% in patients with a partial gastrectomy. More frequent follow-up of these patients should be considered. **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. **Patients with hepatic impairment:** Hepatic impairment has a modest effect on the pharmacokinetics of nilotinib and may lead to an increased exposure with nilotinib. Dose adjustment is not considered necessary in patients with hepatic impairment, however patients with hepatic impairment should be treated with caution. **Paediatric patients**: The safety and efficacy of Tasigna in paediatric patients from birth to less than 18 years have not yet been established therefore its' use in paediatric patients is not recommended.

CONTRAINDICATIONS: Known hypersensitivity to nilotinib or to any of the excipients.

WARNINGS/PRECAUTIONS: Treatment with TASIGNA is associated with thrombocytopenia, neutropenia and anaemia (NCI CTC Grade 3/4). Occurrence is more frequent in patients with imatinib-resistant or intolerant CML, in particular 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. TASIGNA should be used with caution in patients who have or who are at significant risk of developing prolongation of the QT interval. These include patients with congenital long QT interval prolongation, with uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia. Close monitoring for an effect on the QT interval is advisable and a baseline ECG is recommended prior to initiating therapy with Tasigna. Hypokalaemia or hypomagnesaemia should be corrected prior to TASIGNA administration and monitored periodically during therapy. It is recommended that the glucose levels be assessed before initiating treatment with Tasigna and monitored during treatment, as clinically indicated (see section 4.2). If test results warrant therapy, physicians should follow their local standards of practice and treatment guidelines. Uncommon cases (0.1 to 1%) of sudden deaths have been reported in patients with imatinib-resistant or intolerant CML in chronic phase or accelerated phase 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 medicinal products. Ventricular repolarisation abnormalities may have been contributory factors. Women of childbearing potential have to use highly effective contraception during treatment with Tasigna. Severe forms of fluid retention such as pleural effusion, pulmonary oedema, and pericardial effusion were uncommonly (0.1 to 1%) observed in a Phase III study of newly diagnosed CML patients. Similar events were observed in post-marketing reports. Unexpected, rapid weight gain should be carefully investigated. If signs of severe fluid retention appear during treatment with nilotinib, the aetiology should be evaluated and patients treated accordingly. Cardiovascular events were reported in a randomised Phase III study in newly diagnosed CML patients and observed in post-marketing reports. In this clinical study with a median on-therapy time of 48 months, Grade 3-4 cases of cardiovascular events included peripheral arterial occlusive disease (1.1% and 0.4% at 300 mg and 400 mg nilotinib twice daily, respectively), ischaemic heart disease (2.2% and 3.2% at 300 mg and 400 mg nilotinib twice daily, respectively) and ischaemic cerebrovascular events (0.7% and 1.4% at 300 mg and 400 mg nilotinib twice daily, respectively). Patients should be advised to seek immediate medical attention if they experience acute signs or symptoms of cardiovascular events. The cardiovascular status of patients should be evaluated and cardiovascular risk factors monitored and actively managed during Tasigna therapy according to standard guidelines. Appropriate therapy should be prescribed to manage cardiovascular risk factors (see section 4.2 for instructions on managing non-haematological toxicities).

INTERACTIONS: Tasigna may be given in combination with haematopoietic growth factors such as erythropoietin or granulocyte colony-stimulating factor (G-CSF) if clinically indicated. It may be given with hydroxyurea or anagrelide if clinically indicated. 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. If transient interruption of treatment is not possible, close monitoring of the individual for prolongation of the QT interval is indicated (see SPC for full prescribing information). ♦The concomitant administration of other medications that induce CYP3A4 (e.g. phenytoin, carbamazepine, phenobarbital, and St. John's Wort) may reduce exposure to nilotinib. Rifampicin (a potent CYP3A4 inducer) and nilotinib should not be used concomitantly. In patients for whom CYP3A4 inducers are indicated, alternative agents with less enzyme induction potential should be considered. Caution should be exercised when co-administering TASIGNA with substrates of these enzymes (CYP3A4, CYP2C8, CYP2C9, and CYP2D6) that have a narrow therapeutic index. In CML patients, nilotinib administered at 400 mg twice daily for 12 days increased the systemic exposure of oral midazolam (a substrate of CYP3A4). Nilotinib is a moderate CYP3A4 inhibitor. As a result, the systemic exposure of other drugs primarily metabolised by CYP3A4 (e.g. certain HMG-CoA reductase inhibitors) may be increased when co-administered with nilotinib. Tasigna may be used concurrently with esomeprazole or other proton pump inhibitors as needed. Caution is recommended in patients with previous history of pancreatitis. Grapefruit juice and other foods that are known to inhibit CYP3A4 should be avoided. TASIGNA is not recommended for patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

ADVERSE REACTIONS: The following adverse reactions (excluding laboratory abnormalities) were reported in at least 5% of the patients in TASIGNA clinical studies: Headache, Nausea, Constipation, Diarrhoea, Rash, Pruritus, Fatigue, Myalgia, Vomiting, Pain in extremity, Dyspepsia, Decreased appetite **,** Abdominal pain, Upper Abdominal Pain, Alopecia, Arthralgia, Muscle spasms, Bone pain, Asthenia, Peripheral Oedema, Dry Skin, Erythema. The following adverse reactions were reported in patients in the TASIGNA clinical studies at a frequency of less than 5%: ♦ Very common: alanine aminotransferase increased, aspartate aminotransferase increased, lipase increased. hypophosphataemia, hyperbilirubinaemia ♦ Common: eosinophilia, hypertriglyceridaemia, neck pain, lipase increased, xerophthalmia, folliculitis, upper respiratory tract infection (including pharyngitis, nasopharyngitis, rhinitis) skin papilloma, febrile neutropenia, pancytopenia, lymphopenia, electrolyte imbalance (including hypomagnasaemia, hyperkalaemia, hypokalaemia, hyponatraemia, hypocalcaemia, hypercalcaemia, hyperphosphataemia,), diabetes mellitus, hyperglycaemia, hypercholesterolaemia, hyperlipidaemia, decreased appetite, depression, insomnia, anxiety, dizziness, peripheral neuropathy, hypoaesthesia, paraesthesia, eye haemorrhage, periorbital oedema, eye pruritus, conjunctivitis, dry eye, vertigo, angina pectoris, arrythmia (including atroventricular block, cardiac flutter, extrasystoles, tachycardia, atrial fibrillation, bradycardia), palpitations, electrocardiogram QT prolonged, hypertension, flushing, dyspnoea, dyspnoea exertional, epistaxis, cough, dysphonia, pancreatitis, abdominal discomfort, abdominal distension, Dysgeusia, flatulence, hepatic function abnormal, night sweats, eczema, urticaria, erythema, hyperhidrosis, contusion, acne, dermatitis (including allergic and acneiform), dry skin, musculoskeletal chest pain, musculoskeletal pain, back pain, (flank pain), pollakiuria, chest pain (including non -cardiac chest pain), pain (including neck pain and back pain), pyrexia, chest discomfort, malaise, haemoglobin decreased, platelet count decreased blood amylase increased, blood alkaline phosphotase increased, gamma-

glutamyltransferase increased, blood creatinine phosphokinase increased, blood insulin increased, lipoprotein increased (including very low density and high density), weight decreased, weight increased, ♦ Uncommon: intermittent claudication, arterial stenosis limb, intracranial haemorrhage, hypoaesthesia, dehydration, increased appetite, gout, dyslipidaemiahyperthyroidism, hypothyroidism, leukocytosis, pneumonia, urinary tract infections, gastroenteritis, bronchitis, herpes virus infection, candidiasis, globulins decreased, arteriosclerosis, sensitivity of teeth, dyslipidaemia, peripheral arterial occlusive disease, gout, gastritis, toxic hepatitis. ♦Not known: transient ischaemic attack, brain oedema, optic neuritis, lethargy, dysphoria, disorientation, confusional state, amnesia, hyperuricaemia, hypoglycaemia, thrombocythaemia, oral papilloma, sepsis, subcutaneous abscess, anal abscess, furuncle, tine pedis, blood insulin decreased, insulin C-peptide decreased, paraproteinaemia, conjunctival haemorrhage, oropharyngeal pain, hyperkeratosis, psoriasis, hypersensitivity, secondary hyperparathyroidism, thyroiditis. Discontinuation due to adverse drug reactions was observed in 10% of patients. Please refer to the SPC for a full list of all adverse reactions reported.

LEGAL CATEGORY: POM.

MARKETING AUTHORISATION HOLDER: Novartis Europharm Limited, Frimley Business Park, Camberley, GU16 7SR United Kingdom.

MARKETING AUTHORISATION NUMBER: EU/1/07/422/001 – 4.

Please refer to Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available on request from Novartis Pharma Services, P.O. Box 4, MRS 1000, Marsa, Malta. Tel +356 21222872.

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