Summary of Key Safety Recommendations for Tasigna® (nilotinib)

Introduction

The purpose of this brochure is to provide health care professionals prescribing Tasigna® (nilotinib) with the potential serious adverse reactions that may occur with Tasigna therapy and provide information on how to proactively prevent and/or reduce these events.

Tasigna is indicated for

- The treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) in the chronic phase (CP).
- The treatment of adult patients with CP and accelerated phase (AP) Ph+ CML with resistance or intolerance to at least one prior therapy, including imatinib.

The recommended dose of Tasigna for Ph+ CML is:

- 300 mg twice daily for newly diagnosed adult patients in CP.
- 400 mg twice daily for imatinib-resistant or imatinib–intolerant adult patients in CP or AP.

QT prolongation

- Tasigna may prolong the QT interval.
- Prolongation of the QT interval may occur when Tasigna is inappropriately taken with food and/or strong CYP3A4 inhibitors and/or medicinal products known to prolong QT. The presence of hypokalemia and hypomagnesaemia may also further prolong the QT interval.
- Avoid its co-administration with food and concomitant use with strong CYP3A4 inhibitors and/or avoid medicinal products with a known potential to prolong QT.
- Monitor for hypokalaemia and hypomagnesaemia and correct deficiencies.
- Administer Tasigna with caution in patients who are at significant risk of developing QTc prolongation or with long QT syndrome, uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina, or clinically significant bradycardia, or patients taking concomitant antiarrhythmic medicines (including, but not limited to, amiodarone, disopyramide, procainamide, quinidine, and sotalol) or other drugs that may prolong the QT interval (including, but not limited to, chloroquine, halofantrine, clarithromycin, haloperidol, methadone, and moxifloxacin).

Cardiovascular events

- Evaluate the cardiovascular status of patients and actively monitor and manage cardiovascular risk factors during Tasigna therapy according to standard guidelines.
- Advise patients to seek immediate medical attention if they experience acute signs or symptoms of cardiovascular events.

Uncontrolled or significant cardiac disease/cardiac failure

- A baseline ECG is recommended prior to initiating therapy with Tasigna and repeated as clinically indicated.
- Use Tasigna with caution in patients with risk factors for cardiac/coronary heart disease and/or history of uncontrolled or significant cardiac disease. Monitor patient for signs or symptoms consistent with cardiac dysfunction and treat appropriately.

Fluid retention

- Carefully investigate unexpected, rapid weight gain. If signs of severe fluid retention (such as cardiac failure or pulmonary oedema) appear during treatment with Tasigna, evaluate the etiology and treat patients accordingly.

Hepatic transaminase and bilirubin elevations

- Bilirubin and hepatic transaminase levels should be tested monthly or as clinically indicated.

Hepatic impairment

- Hepatic impairment has a modest effect on the pharmacokinetics of Tasigna. Therefore, use with caution in patients with hepatic impairment.

Pancreatitis

- Elevations of lipase and amylase have been observed in patients taking Tasigna. Use with caution in patients with a history of pancreatitis.

Blood glucose increased

- Increases in blood glucose levels have been reported with Tasigna therapy.

Blood cholesterol increased

- Increases in blood cholesterol levels have been reported with Tasigna therapy.

Interaction with food

- Prolongation of the QT interval may occur when nilotinib is inappropriately taken with food. Therefore Tasigna must **NOT** be taken with food. [see QT prolongation]
- Advise patients to avoid food for 2 hours before and at least 1 hour after taking Tasigna.
- Avoid grapefruit juice or other foods that are known to inhibit CYP3A4 while on Tasigna.

Drug interaction with strong CYP3A4 inhibitors

- Tasigna undergoes metabolism by CYP3A4, and concomitant use of strong CYP3A4 inhibitors (including, but not limited to, ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, and ritonavir) can increase the Tasigna serum concentration.
- Should treatment with any of these agents be required, Tasigna therapy should be interrupted if possible. If transient interruption of treatment with Tasigna is not possible, close monitoring of the patient for prolongation of the QT interval is indicated. [see QT prolongation]
- Avoid foods that are known to inhibit CYP3A4, such as grapefruit and grapefruit products, as these may also increase serum concentrations of Tasigna.

Drug interaction with strong CYP3A4 inducers

- Tasigna undergoes metabolism by CYP3A4, and concomitant use of medicinal products that are potent inducers of CYP3A4 may reduce Tasigna serum concentration.
- In patients for whom CYP3A4 inducers (e.g., phenytoin, rifampicin, carbamazepine, phenobarbital, and St. John's Wort) are indicated, consider alternative agents with less enzyme-induction potential.

Interaction with sensitive CYP3A4 substrates

- Monitor patient and dose adjust as needed for drugs that are CYP3A4 substrates and have narrow therapeutic index (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, quinidine, sirolimus and tacrolimus) when co-administered with Tasigna.

Reproductive toxicity/pregnancy

- Tasigna should not be used during pregnancy. If given during pregnancy, the patient must be informed of the potential risk to the fetus.
- Advise women of childbearing potential to use highly effective contraceptives during Tasigna treatment and for up to 2 weeks after treatment.

Special monitoring of Ph+ CML-CP patients who have achieved a sustained deep molecular response

Eligibility for discontinuation of treatment

Discontinuation of Tasigna should be initiated by a physician experienced in the treatment of patients with CML. Eligible patients who are confirmed to express the typical BCR-ABL transcripts, e13a2/b2a2 or e14a2/b3a2, can be considered for treatment discontinuation. Patients must have typical BCRABL transcripts to allow quantitation of BCR-ABL levels, evaluation of the depth of molecular response, and determination of a possible loss of molecular remission after Tasigna treatment discontinuation.

Monitoring of patients who have discontinued therapy

Frequent monitoring of BCR-ABL transcript levels in patients eligible for treatment discontinuation must be performed with a quantitative diagnostic test validated to measure molecular response levels with a sensitivity of at least MR4.5. BCR-ABL transcript levels must be assessed prior to and during treatment discontinuation.

Treatment discontinuation in Ph+ CML-CP patients who have achieved a sustained deep molecular response

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

Please see full prescribing information.

References: 1. TASIGNA® (nilotinib) Core Data Sheet. Basel, Switzerland: Novartis Pharma AG; version 1.5. **2.** TASIGNA® (nilotinib) Summary of Product Characteristics. Basel, Switzerland: Novartis Pharma AG; June 2015.

TASIGNA®

Important note: Before prescribing, consult full prescribing information.

Presentation: Hard capsules containing 200 mg of nilotinib.

Indications: Treatment of adult patients with newly diagnosed philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP). Patients who have been treated with TASIGNA for at least 3 years and have achieved a sustained deep molecular response may be eligible for treatment discontinuation; treatment of adult patients with chronic or accelerated phase (AP) Ph+ CML resistant to or intolerant of at least one prior therapy including imatinib. Ph+ CML patients in chronic phase, who have been previously treated with imatinib and whose treatment has been switched to TASIGNA for at least 3 years and have achieved a sustained deep molecular response may be eligible for treatment discontinuation.

Dosage: ♦Patients with newly diagnosed Ph+ CML-CP: 300 mg twice daily; patients with CP and AP Ph+ CML resistant to or intolerant to at least one prior therapy including imatinib: 400 mg twice daily. ♦Discontinuation of treatment may be considered in eligible Ph+ CML-CP patients who have been treated with TASIGNA for a minimum of 3 years if a deep molecular response is sustained for a minimum of one year immediately prior to discontinuation of therapy. Discontinuation of TASIGNA treatment should be initiated by a physician experienced in the treatment of patients with CML. ♦Increases in blood glucose and serum cholesterol levels have been reported with TASIGNA therapy. Blood glucose levels and lipid profiles should be assessed prior to initiating TASIGNA therapy and monitored during treatment. ♦TASIGNA capsules should be taken twice daily, at approximately 12 hours intervals and must not be taken with food. ♦No food should be consumed for 2 hours before the dose and for at least one hour after the dose. ♦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.

Contraindications: ♦Hypersensitivity to nilotinib or to any of the excipients.

Warnings and precautions: ♦Treatment with TASIGNA associated with thrombocytopenia, neutropenia and anemia, generally reversible and usually managed by withholding TASIGNA temporarily or dose reduction. Complete blood counts to be performed every two weeks for the first 2 months and then monthly thereafter or as clinically indicated. ♦Caution in patients who have or may develop prolongation of QTc (e.g., patients with hypokalemia, hypomagnesemia, congenital long QT syndrome; with uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia; patients taking anti-arrhythmic medicines or other drugs that may lead to QT prolongation). ♦A baseline ECG is recommended prior to initiating therapy with TASIGNA and should be repeated as clinically indicated. ♦Hypokalemia or hypomagnesemia must be corrected prior to TASIGNA administration. ♦Uncommon cases (0.1 to 1%) of sudden death have been reported in clinical trials in patients with significant cardiac risk factors (including ventricular repolarization abnormalities) or with comorbidities/concomitant medications (not in the newly diagnosed Ph+ CML-CP study). The estimated reporting rate for spontaneous reports of sudden death is 0.02% per patient-year. ♦Cardiovascular events (peripheral arterial occlusive disease, ischemic heart disease and ischemic cerebrovascular events) were reported in newly diagnosed Ph+ CML study and observed in the post-marketing reports. If acute signs or symptoms of cardiovascular events occur, advise patients to seek immediate medical attention. The cardiovascular status of patients should be evaluated and cardiovascular risk factors should be monitored and actively managed during TASIGNA therapy according to standard guidelines. ♦Unexpected, rapid weight gain should be carefully investigated. If signs of severe fluid retention appear during treatment with nilotinib, the etiology should be evaluated and patients treated accordingly. ♦It is recommended that the lipid profiles be determined before initiating treatment with TASIGNA, assessed at month 3 and 6 after initiating therapy, and at least yearly during chronic therapy. If a HMG-CoA reductase inhibitor (a lipid lowering agent) is needed, refer to section 8 Interactions, before starting treatment since certain HMG-CoA reductase inhibitors are metabolized by the CYP3A4 pathway. ♦Blood glucose levels should be assessed before initiating treatment with TASIGNA and monitored during treatment. If test results warrant therapy, physicians should follow their local standards of practice and treatment guidelines. ♦Test for hepatitis B infection before initiating treatment with TASIGNA. In patients with positive hepatitis B serology (including those with active disease) and for patients who test positive for hepatitis B infection during treatment, consult experts before initiating treatment. Closely monitor for signs and symptoms of active hepatitis B infection in carriers of hepatitis B virus throughout therapy and for several months following termination of therapy. ♦Must not be taken with food. ♦Eligible patients who are confirmed to express the typical BCR-ABL transcripts, can be considered for treatment discontinuation. Monitoring of BCR-ABL transcript levels in patients eligible for treatment discontinuation must be performed with a quantitative diagnostic test validated to measure molecular response levels with a sensitivity of at least MR4.5. BCR-ABL transcript levels must be assessed prior to and during treatment discontinuation. Frequent monitoring of BCR-ABL transcript levels and complete blood count with differential is required to detect possible loss of remission. ♦Avoid grapefruit juice and other foods that are known to inhibit CYP3A4. ♦Caution in patients with hepatic impairment. ♦Caution in patients with previous history of pancreatitis. Interrupt treatment in case of lipase elevations accompanied by abdominal symptoms. ♦The bioavailability of nilotinib might be reduced in patients with total gastrectomy. ♦Due to possible occurrence of tumor lysis syndrome, correction of clinically significant dehydration and treatment of high uric acid levels are recommended prior TASIGNA administration. ♦Not recommended in patients with rare hereditary problems of galactose intolerance, of severe lactase deficiency or of glucose-galactose malabsorption.

Pregnancy: ♦Women of child-bearing potential must use highly effective method of contraception while receiving TASIGNA and for up to 2 weeks after ending treatment. ♦Should not be used during pregnancy unless clearly necessary.

Breast-feeding: ♦Breast-feeding is not recommended.

Interactions: ♦Avoid in patients treated with medicines known to prolong the QT interval (e.g., chloroquine, methadone, halofantrine, clarithromycin, haloperidol, moxifloxacin, bepridil, pimozide). ♦Avoid in patients treated with anti-arrhythmic medicines (e.g. amiodarone, disopyramide, procainamide, quinidine, sotalol). ♦Avoid administration of strong CYP3A4 inhibitors (e.g. ketoconazole, ritonavir, itraconazole, voriconazole, telithromycin). ♦Caution with CYP3A4 inducers (e.g., phenytoin, rifampicin, carbamazepine, phenobarbital, or St. John's Wort). ♦TASIGNA may be used concurrently with esomeprazole or other proton pump inhibitors. ♦TASIGNA can be used concurrently with warfarin. ♦Caution with medicines that affect P-glycoprotein. ♦Nilotinib is a moderate CYP3A4 inhibitor. The systemic exposure of other drugs primarily metabolized by CYP3A4 (e.g. 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. ♦Avoid grapefruit juice and other foods that are known to inhibit CYP3A4. ♦In concurrent use: the H2 blocker (e.g. famotidine) may be administered approximately 10 hours before and approximately 2 hours after TASIGNA dose; antacids (e.g., aluminum hydroxide, magnesium hydroxide, simethicone) may be administered approximately 2 hours before or approximately 2 hours after TASIGNA dose.

Adverse drug reactions:

Very common: headache, nausea, constipation, vomiting, abdominal pain upper, rash, pruritus, alopecia, myalgia, arthralgia, fatigue, myelosuppression (thrombocytopenia, neutropenia, anaemia), hypophosphataemia (including blood phosphorus decreased), hyperbilirubinaemia (including blood bilirubin increased), alanine aminotransferase increased, aspartate aminotransferase increased, lipase increased, lipoprotein cholesterol (including low density and high density) increased, total cholesterol increased, blood triglycerides increased, musculoskeletal pain, myalgia, pain in extremity, arthralgia, bone pain and spinal pain upon discontinuing treatment with TASIGNA.

Common: folliculitis, upper respiratory tract infection (including pharyngitis, nasopharyngitis, rhinitis), skin papilloma, leukopenia, eosinophilia, febrile neutropenia, pancytopenia, lymphopenia, anorexia, electrolyte imbalance (including hypomagnesaemia, hyper/hypokalaemia, hyponatraemia, hyper/hypocalcaemia, 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 (including xerophthalmia), vertigo, angina pectoris, arrhythmia (including atrioventricular block, cardiac flutter, extrasystoles, atrial fibrillation, tachycardia, bradycardia), palpitations, electrocardiogram QT prolonged, hypertension, flushing, dyspnoea, dyspnoea exertional, epistaxis, cough, dysphonia, abdominal pain, diarrhoea, pancreatitis, abdominal discomfort/distension, dyspepsia, dysgeusia, flatulence, hepatic function abnormal, night sweats, eczema, urticaria, hyperhidrosis, contusion, acne, dermatitis (including allergic exfoliative and acneiform), muscle spasms, bone pain, pain in extremity, musculoskeletal chest pain, musculoskeletal pain, back pain, neck pain, flank pain, muscular weakness, pollakiuria, asthenia, oedema peripheral, pyrexia, chest pain (including non-cardiac chest pain), pain, chest discomfort, malaise, haemoglobin decreased, blood amylase increased, gamma-glutamyltransferase increased, blood creatine phosphokinase increased, blood alkaline phosphatase increased, blood insulin increased, weight decreased, weight increased, globulins decreased.

Uncommon: pneumonia, urinary tract infections, gastroenteritis, bronchitis, herpes virus infection, candidiasis including oral candidiasis, hyperthyroidism, hypothyroidism, gout, dehydration, increased appetite, dyslipidaemia, intracranial haemorrhage, ischaemic stroke, transient ischaemic attack, cerebral infarction, migraine, loss of consciousness (including syncope), tremor, disturbance of attention, hyperaesthesia, vision impairment, vision blurred, visual acuity reduced, eyelid oedema, photopsia, hyperaemia (scleral, conjunctival, ocular), eye irritation, conjunctival haemorrhage, cardiac failure, myocardial infarction, coronary artery disease, cardiac murmur, pleural and pericardial effusions, cyanosis, hypertensive crisis, peripheral arterial occlusive disease, intermittent claudication, arterial stenosis limb, haematoma, arteriosclerosis, pulmonary oedema, interstial lung disease, pleuric pain, pleurisy, pharyngolaryngeal pain, throat irriation, gastrointestinal haemorrhage, melena, mouth ulceration, gastroesophageal reflux, stomatitis, oesophageal pain, dry mouth, gastritis, sensitivity of teeth, hepatotoxicity, toxic hepatitis, jaundice, exfoliative rash, drug eruption, pain of skin, ecchymosis, swelling face, musculoskeletal stiffness, joint swelling, dysuria, micturation urgency, nocturia, breast pain, gynaecomastia, erectile dysfunction, face oedema (including swelling face), gravitational oedema, influenza-like illness, chills, feeling body temperature change (including feeling hot, feeling cold), blood lactate dehydrogenase increased, blood urea increased.

Frequency not known: sepsis, subcutaneous abscess, anal abscess, furuncle, tinea pedis, oral papilloma, paraproteinaemia, thrombocythaemia, leukocytosis, hypersensitivity, hyperparathyroidism secondary, thyroiditis, hyperuricaemia, hypoglycaemia, disorientation, confusional state, amnesia, dysphoria, cerebrovascular accident, basilar artery stenosis, brain oedema, optic neuritis, lethargy, dysaesthesia, restless legs syndrome, papilloedema, diplopia, photophobia, eye swelling, blepharitis, eye pain, chorioretinopathy, conjunctivitis allergic, ocular surface disease, hearing impaired, ear pain, tinnitus, ventricular dysfunction, pericarditis, ejection fraction decreased, shock haemorrhagic, hypotension, thrombosis, peripheral artery stenosis, pulmonary hypertension, wheezing, oropharyngeal pain, gastrointestinal ulcer perforation, retroperitoneal haemorrhage, haematemesis, gastric ulcer, oesophagitis ulcerative, subileus, enterocolitis, haemorrhoids, hiatus hernia, rectal haemorrhage, gingivitis, cholestasis, hepatomegaly, psoriasis, erythema multiforme, erythema nodosum, skin ulcer, palmar-plantar erythrodysaesthesia syndrome, petechiae, photosensitivity, blister, dermal cyst, sebaceous hyperplasia, skin atrophy, skin discolouration, skin exfoliation, skin hyperpigmentation, skin hypertrophy, hyperkeratosis, arthritis, renal failure, haematuria, urinary incontinence, chromaturia, breast induration, menorrhagia, nipple swelling, localized oedema, troponin increased, blood bilirubin unconjugated increased, blood insulin decreased, insulin C-peptide decreased, blood parathyroid hormone increased, tumour lysis syndrome, and hepatitis B reactivation.

you can report any undesirable effects through:
- **Toll free phone: 8002490000**
- **Fax: +966-11-205-7662**
- **E-mail: npc.drug@sfda.gov.sa**
- **Or by online: https://ade.sfda.gov.sa/**

Or Novartis drug safety:
Phone: +99611 265 8100
Fax: +966 11 265 8107
Email: adverse.events@novartis.com

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