Important Safety Information about TASIGNA®

**Important note:** Before prescribing, consult full prescribing information.

**Presentation:** Hard capsules containing 150 mg or 200 mg of nilotinib.

**Indications:** Treatment of adult patients with newly diagnosed philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP); treatment of adult patients with chronic or accelerated phase (AP) Ph+ CML resistant to or intolerant of at least one prior therapy including imatinib.

**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. ♦ 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 approximately 12 hours apart 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/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 as clinically indicated. ● Hypokalaemia or hypomagnesaemia must be corrected prior to Tasigna administration and should be monitored periodically during therapy. ● 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. ● 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 (peripheral arterial occlusive disease, ischemic heart disease and ischemic cerebrovascular 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. ● 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 required, refer to section 4.5 before initiating treatment since certain HMG-CoA reductase inhibitors are metabolised by the CYP3A4 pathway. ● Blood glucose levels should be assessed before initiating treatment with Tasigna and monitored during treatment, as clinically indicated. If test results warrant therapy, physicians should follow their local standards of practice and treatment guidelines. ● Must not be taken with food. ● 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 to initiating therapy with Tasigna. ● Not recommended in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or of glucose-galactose malabsorption.

Pregnancy: ● Women of child-bearing potential must use highly effective contraception during treatment with 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 metabolised 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, cyclopamine, 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 reactions: Very common: headache, nausea, constipation, diarrhoea, vomiting, rash, pruritus, alopecia, myalgia, fatigue, upper abdominal pain, myelosuppression (thrombocytopenia, neutropenia, anemia), hypophosphataemia (including blood phosphorus decreased), hyperbilirubinemia (including blood bilirubin increased), alanine aminotransferase increased, aspartate aminotransferase increased, lipase increased, lipoprotein cholesterol increased (including low density and high density), total cholesterol increased, blood triglycerides increased.

Common: folliculitis, upper respiratory tract infection (including pharyngitis, nasopharyngitis, rhinitis), skin papilloma, leukopenia, eosinophilia, febrile neutropenia, pancytopenia, lymphopenia, hyperthyroidism, hypothyroidism, anorexia, electrolyte imbalance (including hypomagnesemia, hyper/hypokalemia, hyponatremia, hyper/hypocalcemia, hyperphosphatemia), diabetes mellitus, hyperglycaemia, hypercholesterolaemia, hyperlipidaemia, hypertriglyceridaemia, decreased appetite, depression, insomnia, anxiety, dizziness, peripheral neuropathy, hypoesthesia, paresthesia, 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, myocardial infarction, hypertension, flushing, peripheral artery stenosis, dyspnoea, dyspnoea exertional, epistaxis, cough, dysphonia, abdominal pain, pancreatitis, abdominal discomfort/distension, dyspepsia, dysgeusia, flatulence, hepatic function abnormal, night sweats, eczema, urticaria, hyperhidrosis, cutaneous, acne, dermatitis (including allergic exfoliative and acneiform), dry skin, erythema, arthralgia, muscle spasms, bone pain, pain in extremity, musculoskeletal chest pain, musculoskeletal pain, back pain, neck pain, flank pain, muscular weakness, polyuria, 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, thrombocythaemia, leukocytosis, 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, pleural and pericardial effusions, coronary artery disease, cyanosis, cardiac murmur, hypertensive crisis, peripheral arterial occlusive
disease, intermittent claudication, arterial stenosis limb, haematoma, arteriosclerosis, pulmonary oedema, interstitial lung disease, pleuric pain, pleurisy, pharyngolaryngeal pain, throat irritation, gastrointestinal haemorrhage, melaena, mouth ulceration, gastrooesophageal reflux, stomatitis, oesophageal pain, dry mouth, gastritis, sensitivity of teeth, hepatotoxicity, toxic hepatitis, jaundice, exfoliative rash, drug eruption, skin pain, 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.

Unknown frequency: sepsis, subcutaneous abscess, anal abscess, furuncle, tinea pedis, oral papilloma, paraproteinaemia, 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, 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 discoloration, 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, tumor lysis syndrome.

Packs and prices: Country specific.

Legal classification: Country specific.