Important Safety Information about TASIGNA®

Important note: Before prescribing, consult full prescribing information.

Presentation: Hard capsules containing 50 mg, 150 mg or 200 mg of nilotinib.

Indications: Treatment of adult and paediatric 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. Efficacy data in patients with CML in blast crisis are not available. Treatment of paediatric patients with chronic phase Philadelphia chromosome positive CML with resistance or intolerance to prior therapy including imatinib.

Dosage: ♦Please see the nilotinib Summary of Product Characteristics. **Click here to access**.

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 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). ♦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. ♦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. ♦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. ♦Eligible patients who are confirmed to express the typical BCR-ABL transcripts, e13a2/b2a2 or e14a2/b3a2, can be considered for treatment discontinuation. 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/ABL ≤0.0032% IS). BCR-ABL transcript levels must be assessed prior to and during treatment discontinuation. Loss of major molecular response (MMR; BCR-ABL/ABL ≤0.1%IS) or confirmed loss of MR4.0 (two consecutive measures separated by at least 4 weeks showing loss of MR4.0 (BCR-ABL/ABL ≤0.01%IS)) will trigger treatment re-initiation within 4 weeks of when loss of remission is known to have occurred. It is crucial to perform frequent monitoring of BCR-ABL transcript levels and complete blood count with differential in order to detect possible loss of remission. For patients who fail to achieve MMR after three months of treatment re initiation, BCR-ABL kinase domain mutation testing should be performed. ♦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 4.5 Interactions section of the Summary of Product Characteristics 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. ♦Must not be taken with food. No food should be consumed for 2 hours before the dose and for at least one hour after ♦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.♦Should not be used in patients with rare hereditary problems of

galactose intolerance, of severe lactase deficiency or of glucose-galactose malabsorption. ♦In paediatric patients the long-term effects of prolonged treatment with Tasigna are unknown.

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. ♦If pregnancy is planned during the treatment-free remission phase, the patient must be informed of a potential need to re-initiate treatment with Tasigna during pregnancy.

Breast-feeding: ♦Should not be used during breast-feeding.

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. Control of warfarin pharmacodynamic markers (INR or PT) is recommended ♦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 reactions: ♦**Very common**: headache, nausea, constipation, diarrhoea, vomiting, abdominal pain upper, rash, pruritus, alopecia, myalgia, fatigue, myelosuppression (thrombocytopenia, neutropenia, anemia), hypophosphatemia (including blood phosphorus decreased), hyperbilirubinemia (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 within the framework of attempting treatment free remission.

♦**Common**: folliculitis, upper respiratory tract infection (including pharyngitis, nasopharyngitis, rhinitis), skin papilloma, leukopenia, eosinophilia, febrile neutropenia, pancytopenia, lymphopenia, thrombocythaemia, leukocytosis, anorexia, electrolyte imbalance (including hypomagnesemia, hyper/hypokalemia, hyponatremia, hyper/hypocalcemia, hyperphosphatemia), diabetes mellitus, hyperglycemia, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, decreased appetite, depression, insomnia, anxiety, dizziness, peripheral neuropathy, hypoesthesia, paresthesia, eye hemorrhage, periorbital edema, 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, peripheral artery stenosis, dyspnea, dyspnea exertional, epistaxis, cough, dysphonia, abdominal pain, diarrhea, 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, arthralgia, bone pain, pain in extremity, musculoskeletal chest pain, musculoskeletal pain, back pain, neck pain, flank pain, muscular weakness, pollakiuria, asthenia, edema peripheral, pyrexia, chest pain (including

non-cardiac chest pain), pain, chest discomfort, malaise, hemoglobin 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, dyslipidemia, intracranial hemorrhage, ischemic stroke, transient ischemic attack, cerebral infarction, migraine, loss of consciousness (including syncope), tremor, disturbance of attention, hyperesthesia, vision impairment, vision blurred, visual acuity reduced, eyelid edema, photopsia, hyperemia (scleral, conjunctival, ocular), eye irritation, conjunctival hemorrhage, 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, hematoma, arteriosclerosis, pulmonary edema, interstitial lung disease, pleuric pain, pleurisy, pharyngolaryngeal pain, throat irritation, gastrointestinal hemorrhage, melena, mouth ulceration, gastroesophageal reflux, stomatitis, esophageal 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, micturition urgency, nocturia, breast pain, gynecomastia, erectile dysfunction, face edema (including swelling face), gravitational edema, influenza-like illness, chills, feeling body temperature change (including feeling hot, feeling cold), blood lactate dehydrogenase increased, blood glucose decreased, blood urea increased.

♦**Frequency not known**: sepsis, subcutaneous abscess, anal abscess, furuncle, tinea pedis, oral papilloma, paraproteinemia, hypersensitivity, hyperparathyroidism secondary, thyroiditis, hyperuricemia, hypoglycemia, disorientation, confusional state, amnesia, dysphoria, cerebrovascular accident, brain edema, optic neuritis, lethargy, dysesthesia, 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 hemorrhagic, hypotension, thrombosis, pulmonary hypertension, wheezing, oropharyngeal pain, gastrointestinal ulcer perforation, retroperitoneal hemorrhage, hematemesis, gastric ulcer, esophagitis ulcerative, subileus, enterocolitis, hemorrhoids, hiatus hernia, rectal hemorrhage, gingivitis, cholestasis, hepatomegaly, psoriasis, erythema multiforme, erythema nodosum, skin ulcer, palmar-plantar erythrodysesthesia syndrome, petechiae, photosensitivity, blister, dermal cyst, sebaceous hyperplasia, skin atrophy, skin discoloration, skin exfoliation, skin hyperpigmentation, skin hypertrophy, hyperkeratosis, arthritis, renal failure, hematuria, urinary incontinence, chromaturia, breast induration, menorrhagia, nipple swelling, localized edema, troponin increased, blood bilirubin unconjugated increased, blood insulin decreased, insulin C-peptide decreased, blood parathyroid hormone increased, and hepatitis B reactivation.