

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. ♦ TASIGNA® capsules should be taken twice daily at an interval of 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 (eg, 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). ♦ 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. ♦ 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. ♦ 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. ♦ Must not be taken with food. ♦ Avoid grapefruit juice and other foods that are known to inhibit CYP3A4. ♦ Should not be used during pregnancy unless clearly necessary. ♦ Breast-feeding not recommended ♦ Not recommended in patients with rare hereditary problems of galactose intolerance, of severe lactase deficiency or of glucose-galactose malabsorption. ♦ 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. ♦The bioavailability of nilotinib might be reduced in patients with total gastrectomy.

Interactions: ♦ Avoid in patients treated with medicines known to prolong the QT interval (eg, chloroquine, methadone, halofantrine, clarithromycin, haloperidol, moxifloxacin, bepridil, pimozide). ♦ Avoid in patients treated with anti-arrhythmic medicines (eg, amiodarone, disopyramide, procainamide, quinidine, sotalol). ♦ Administration of strong CYP3A4 inhibitors (eg, ketoconazole, ritonavir, itraconazole, voriconazole, telithromycin) to be avoided. ♦ Caution with CYP3A4 inducers (eg, 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. ♦ Single-dose administration of TASIGNA with midazolam increased midazolam exposure by 30%, however the metabolic ratio of 1-hydroxymidazolam to midazolam was not altered. ♦ Caution with medicines that affect P-glycoprotein. ♦ Avoid grapefruit juice and other foods that are known to inhibit CYP3A4.

Adverse reactions: ♦ **Very common:** headache, nausea, constipation, diarrhea, vomiting, rash, pruritus, alopecia, myalgia, fatigue, myelosuppression (thrombocytopenia, neutropenia, anemia), lipase increased.

♦ **Common:** folliculitis, skin papilloma, febrile neutropenia, pancytopenia, lymphopenia, anorexia, electrolyte imbalance (including hypomagnesemia, hyper/hypokalemia, hyponatremia, hyper/hypocalcemia, hyper/hypophosphatemia), diabetes mellitus, hyperglycemia, hypercholesterolemia, hyperlipidemia, decreased appetite, depression, insomnia, anxiety, dizziness, peripheral neuropathy, hypoesthesia, paresthesia, eye hemorrhage, periorbital edema, eye pruritus, conjunctivitis, dry eye, vertigo, angina pectoris, arrhythmia (including atrioventricular block, cardiac flutter, extrasystoles, atrial fibrillation, tachycardia, bradycardia), palpitations, electrocardiogram QT prolonged, hypertension, flushing, dyspnea, dyspnea exertional, epistaxis, cough, dysphonia, abdominal pain/abdominal pain upper, pancreatitis, abdominal discomfort/distension, dyspepsia, dysgeusia, flatulence, hepatic function abnormal, night sweats, eczema, urticaria, hyperhidrosis, contusion, acne, dermatitis (including allergic and acneiform), dry skin, erythema, arthralgia, muscle spasms, bone pain, pain in extremity, musculoskeletal chest pain, musculoskeletal pain, flank pain, pollakiuria, asthenia, edema peripheral, pyrexia, chest pain (including non-cardiac chest pain), pain (including neck pain and back pain), chest discomfort, malaise, hemoglobin decreased, blood amylase increased, gamma-glutamyltransferase increased, blood creatinine phosphatase increased, blood alkaline phosphatase increased, elevated AST/ALT, hypophosphatemia, elevated bilirubin, weight decreased, weight increased.

♦ **Uncommon:** upper respiratory tract infection (including nasopharyngitis, rhinitis), pneumonia, urinary tract infections, gastroenteritis, bronchitis, herpes virus infection, candidiasis including oral candidiasis, hyperthyroidism, hypothyroidism, dehydration, increased appetite, intracranial hemorrhage, 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, cardiac failure, pleural and pericardial effusions, coronary artery disease, cyanosis, cardiac murmur, hypertensive crisis, hematoma, pulmonary edema, interstitial lung disease, pleuric pain, pleurisy, pharyngolaryngeal pain, throat

irritation, gastrointestinal hemorrhage, melena, mouth ulceration, gastroesophageal reflux, stomatitis, esophageal pain, dry mouth, hepatotoxicity, hepatitis, jaundice, exfoliative rash, drug eruption, pain of skin, ecchymosis, swelling face, musculoskeletal stiffness, muscular weakness, joint swelling, dysuria, micturation 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 urea increased.

◆ **Unknown frequency:** sepsis, subcutaneous abscess, anal abscess, furuncle, tinea pedis, oral papilloma, thrombocytopenia, leukocytosis, eosinophilia, hypersensitivity, hyperparathyroidism secondary, thyroiditis, hyperuricemia, gout, hypoglycemia, dyslipidemia, disorientation, confusional state, amnesia, dysphoria, brain edema, optic neuritis, lethargy, dysesthesia, restless legs syndrome, papilledema, diplopia, photophobia, eye swelling, blepharitis, eye pain, chorioretinopathy, conjunctival hemorrhage, conjunctivitis allergic, ocular surface disease, hearing impaired, ear pain, tinnitus, myocardial infarction, ventricular dysfunction, pericarditis, ejection fraction decreased, shock hemorrhagic, arteriosclerosis obliterans, hypotension, thrombosis, pulmonary hypertension, wheezing, gastrointestinal ulcer perforation, retroperitoneal hemorrhage, hematemesis, gastric ulcer, esophagitis ulcerative, subileus, gastritis, enterocolitis, hemorrhoids, hiatus hernia, rectal hemorrhage, sensitivity of teeth, gingivitis, cholestasis, hepatomegaly, erythema multiforme, erythema nodosum, skin ulcer, palmar-plantar erythrodysesthesia syndrome, petechia, photosensitivity, blister, dermal cyst, sebaceous hyperplasia, skin atrophy, skin discolouration, skin exfoliation, skin hyperpigmentation, skin hypertrophy, arthritis, renal failure, hematuria, urinary incontinence, chromaturia, breast induration, menorrhagia, nipple swelling, localised edema, troponin increased, blood bilirubin unconjugated increased, blood insulin increased, lipoprotein increased (including very low density and high density), blood parathyroid hormone increased, tumor lysis syndrome.

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