Prescribing Information:
TASIGNA® (nilotinib)

Important note: Before prescribing, consult Summary of Product Characteristics (SmPC).

Presentation: Nilotinib 50, 150 and 200mg capsules.
I**ndication(s)**: Adult and paediatric patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) in the chronic phase. Adult patients with chronic phase and accelerated phase Ph+ CML with resistance or intolerance to prior therapy including imatinib. Paediatric patients with chronic phase Ph+ CML with resistance or intolerance to prior therapy including imatinib.
Dosage and administration: Twice daily, orally, approximately 12 hours apart. Must not be taken with food. *Adults*: 300mg twice daily in newly diagnosed patients with CML in the chronic phase. 400mg twice daily in patients with chronic or accelerated phase CML with resistance or intolerance to prior therapy. *Children*: 230mg/m^2 twice daily, rounded to the nearest 50mg dose (to a maximum single dose of 400mg). There is no experience with treatment below 2 years of age. There are no data in newly diagnosed patients below 10 years of age and limited data in imatinib-resistant or intolerant patients below 6 years of age.
Discontinuation of treatment may be considered in eligible Ph+ CML patients in chronic phase who have been treated with Tasigna for a minimum of 3 years if a deep molecular response (MR4.5) is sustained for a minimum of one year immediately prior to discontinuation of therapy. Refer to the SmPC for monitoring requirements. Tasigna may need to be temporarily withheld and/or dose reduced for haematological toxicities (neutropenia, thrombocytopenia) that are not related to the underlying leukaemia. If clinically significant moderate or severe non-haematological toxicity develops, dosing should be interrupted, and patients should be monitored and treated accordingly. Refer to the SmPC for dose adjustments.
Contraindications: Hypersensitivity to the active substance or to any of the excipients.
Warnings/Precautions: *Myelosuppression*: Treatment is associated with thrombocytopenia, neutropenia and anaemia more frequently in patients with imatinib-resistant or intolerant CML, in particular in patients with accelerated phase CML. Complete blood counts should be performed every two weeks for the first 2 months and then monthly thereafter. *QT prolongation*: Tasigna should be used with caution in patients who have, or who are at significant risk of developing prolongation of the QTc interval. Close monitoring for an effect on the QTc interval and a baseline ECG is recommended prior to initiating therapy and as clinically indicated. Hypokalaemia or hypomagnesaemia must be corrected prior to Tasigna administration and monitored periodically during therapy. *Sudden death*: Uncommon cases of sudden deaths have been reported in patients with a past medical history of cardiac disease or significant cardiac risk factors. *Fluid retention and oedema*: Severe forms of fluid retention such as pleural effusion, pulmonary oedema, and pericardial effusion were uncommonly observed in newly diagnosed CML patients. Unexpected, rapid weight gain should be carefully investigated. *Cardiovascular events*: 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. *Blood lipids, glucose and serum lipase*: Increases in total serum cholesterol, glucose and serum lipase have been reported. Determine lipid profiles before initiating treatment, at month 3 and 6 and at least yearly during chronic therapy. Assess glucose levels before initiating treatment and monitor during treatment. Caution is recommended in patients with previous history of pancreatitis. *Reactivation of Hepatitis B*: Reactivation of HBV has been reported and some cases resulted in acute hepatic complications, liver transplantation or a fatal outcome. Test for HBV before treatment initiation. Carriers of HBV should be closely monitored for HBV infection during therapy and after therapy for several months. *Tumour lysis syndrome (TLS)*: Correct dehydration and treat high uric acid levels prior to treatment. *Total gastrectomy*: Bioavailability might be reduced in patients with total gastrectomy. *Lactose*: Tasigna capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. *Paediatric population*: Laboratory abnormalities of mild to moderate transient elevations of aminotransferases and total bilirubin have been observed in children at a higher frequency than in adults, indicating a higher risk of hepatotoxicity in the paediatric population. Liver function (bilirubin and hepatic transaminases levels) should be monitored monthly or as clinically indicated. Growth retardation has been documented in patients treated with nilotinib. Close monitoring of growth in paediatric patients is recommended.
Interactions: Concomitant treatment with strong CYP3A4 inhibitors, including ketoconazole, itraconazole, voriconazole, ritonavir, clarithromycin, and telithromycin, should be avoided. Increased exposure to nilotinib might also be expected with moderate CYP3A4 inhibitors. The concomitant administration of CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbital and St. John's Wort) is likely to reduce exposure to nilotinib to a clinically relevant extent. *In vitro*, nilotinib is a relatively strong inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2D6 and UGT1A1. Control of warfarin markers (INR or PT) following initiation of nilotinib therapy (at least during the first 2 weeks) is recommended. Appropriate monitoring and dose adjustment may be necessary for CYP3A4 substrates that have a narrow therapeutic index (eg. alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, sirolimus and tacrolimus). Nilotinib should be used with caution in patients taking anti-arrhythmic medicinal products such as amiodarone, disopyramide, procainamide, quinidine and sotalol or other medicinal products that may lead to QT prolongation such as chloroquine, halofantrine, clarithromycin, haloperidol, methadone and moxifloxacin. The absorption and bioavailability of nilotinib are increased if it is taken with food. Grapefruit juice and other foods that are known to inhibit CYP3A4 should be avoided.
Fertility, pregnancy and lactation: Use effective contraception. Do not use during pregnancy unless clearly necessary. If it is used during pregnancy, the patient must be informed of the potential risk to the foetus. Women taking Tasigna should not breast-feed during treatment and for 2 weeks after the last dose.

Undesirable effects: *Very common (≥1/10)*: headache, nausea, constipation, diarrhoea, upper abdominal pain, rash, pruritus, fatigue, myalgia, alopecia, vomiting, 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. *Common (≥1/100 to <1/10)*: folliculitis, upper respiratory tract infection (including pharyngitis, nasopharyngitis, rhinitis), skin papilloma, leukopenia, eosinophilia, febrile neutropenia, pancytopenia, lymphopenia, decreased appetite, electrolyte imbalance (including hypomagnesaemia, hyperkalaemia, hypokalaemia, hyponatraemia, hypocalcaemia, hypercalcaemia, hyperphosphataemia), diabetes mellitus, hyperglycaemia, hypercholesterolaemia, hyperlipidaemia, hypertriglyceridaemia, depression, insomnia, anxiety, dizziness, peripheral neuropathy, hypoaesthesia, paraesthesia, eye haemorrhage, periorbital oedema, eye pruritus, conjunctivitis, dry eye (including xerophthalmia), vertigo, angina pectoris, arrhythmia (including atroventricular block, cardiac flutter, extrasystoles, tachycardia, atrial fibrillation, bradycardia), palpitations, electrocardiogram QT prolonged, hypertension, flushing, peripheral artery stenosis, dyspnoea, dyspnoea exertional, epistaxis, cough, dysphonia, abdominal pain, dyspepsia, pancreatitis, abdominal discomfort, abdominal distension, dysgeusia, flatulence, hepatic function abnormal, dry skin, erythema, 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, flank pain, neck pain, muscular weakness, pollakiuria, asthenia, peripheral oedema, chest pain (including non-cardiac chest pain), pain, pyrexia, chest discomfort, malaise, haemoglobin decreased, blood insulin increased, globulins decreased, blood amylase increased, blood alkaline phosphatase increased, gamma-glutamyltransferase increased, blood creatinine phosphokinase increased, weight decreased, weight increased. *Uncommon (≥1/1,000 to <1/100)*: pneumonia, urinary tract infection, gastroenteritis, bronchitis, herpes virus infection, candidiasis (including oral candidiasis), thrombocythaemia, leukocytosis, hyperthyroidism, hypothyroidism, dyslipidaemia, intracranial haemorrhage, ischaemic stroke, transient ischaemic attack, cerebral infarction, loss of consciousness (including syncope), hyperaesthesia, visual impairment, conjunctival haemorrhage, visual acuity reduced, eyelid oedema, cardiac failure, myocardial infarction, coronary artery disease, cardiac murmur, pericardial effusion, cyanosis, hypertensive crisis, peripheral arterial occlusive disease, intermittent claudication, arterial stenosis limb, haematoma, arteriosclerosis, pulmonary oedema, pleural effusion, interstitial lung disease, pleurisy, gastrointestinal haemorrhage, melaena, stomatitis, gastritis, hepatotoxicity, toxic hepatitis, jaundice, swelling face, face oedema, blood lactate dehydrogenase increased, blood glucose decreased, blood urea increased. *Not known*: sepsis, subcutaneous abscess, anal abscess, hepatitis B reactivation, oral papilloma, paraproteinaemia, hypersensitivity, thyroiditis, hyperuricaemia, hypoglycaemia, amnesia, cerebrovascular accident, brain oedema, optic neuritis, papilloedema, chorioretinopathy, diplopia, eye swelling, ocular surface disease, ventricular dysfunction, pericarditis, ejection fraction decreased, shock haemorrhagic, hypotension, thrombosis, pulmonary hypertension, gastrointestinal ulcer perforation, retroperitoneal haemorrhage, haematemesis, gastric ulcer, oesophagitis ulcerative, subileus, enterocolitis, hiatus hernia, rectal haemorrhage, cholestasis, hepatomegaly, erythema multiforme, skin ulcer, arthritis, renal failure, localised oedema, troponin increased, blood bilirubin unconjugated increased, blood insulin decreased, insulin C-peptide decreased, blood parathyroid hormone increased, tumour lysis syndrome.
Other Adverse Effects: Please consult the Summary of Product Characteristics for a detailed listing of all adverse events before prescribing.
Legal classification: POM
Marketing Authorisation number, quantities and NHS price:
EU/1/07/422/015 – 50mg x 120 capsules, £2,432.85
EU/1/07/422/006 – 150mg x 112 capsules, £2,432.85
EU/1/07/422/008 – 200mg x 112 capsules, £2,432.85
Date of last revision of prescribing information: **November 2019 TAS19-C037**

Full Prescribing Information available from: Novartis Pharmaceuticals UK Ltd, Frimley Business Park, Frimley, Camberley, Surrey, GU16 7SR. Tel: 01276 692255, Fax: 01276 692508.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.UK/yellowcard. Adverse events should also be reported to Novartis via uk.patientsafety@novartis.com or online through the patient safety information (PSI) tool at https://psi.novartis.com

If you have a question about the product, please contact Medical Information on 01276 698370 or by email at medinfo.uk@novartis.com

UK Prescribing Information:
GLIVEC® ▼ (imatinib) 100mg and 400mg Tablets

Important note: Before prescribing, consult Summary of Product Characteristics (SmPC).

Presentation: Imatinib (as mesilate) 100 mg and 400 mg film-coated tablets
Indication(s): Chronic myeloid leukaemia (CML) Treatment of adult and paediatric patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) CML for whom bone marrow transplantation is not considered as the first line of treatment. Treatment of adult and paediatric patients with Ph+ CML in chronic phase after failure of interferon-alfa therapy or in accelerated phase or blast crisis. Gastrointestinal stromal tumours (GIST) Treatment of adult patients with Kit (CD 117) positive unresectable and/or metastatic malignant GIST. Adjuvant treatment of adult patients who are at significant risk of relapse following resection of Kit (CD117)-positive GIST. Patients who have a low or very low risk of recurrence should not receive adjuvant treatment.
Dosage and administration: Oral with a meal. CML *Adults:* 400mg/day for patients in chronic phase CML and 600mg/day for patients in accelerated phase or blast crisis. Increases to 800mg (given as 400mg twice daily) may be considered. *Children:* 340mg/m^2 daily. Increases to 570mg/m^2 daily (not to exceed the total dose of 800mg) may be considered. There is no experience with the treatment of children below 2 years of age.
GIST: The recommended dosage is 400mg/day.
Refer to the SmPC for dose adjustments due to adverse reactions. Patients with liver dysfunction or renal insufficiency should be given the minimum recommended dose of 400mg daily.
Contraindications: Hypersensitivity to the active substance or to any of the excipients.
Warnings/Precautions: *Hypothyroidism:* Use with caution in patients receiving levothyroxine, closely monitor TSH levels. *Hepatotoxicity:* Cases of liver injury, including hepatic failure and hepatic necrosis, have been observed with imatinib. *Fluid retention*: Occurrences of severe fluid retention have been reported. Weigh patients regularly. *Cardiac disease:* Patients with cardiac disease or risk factors for cardiac failure or history of renal failure should be monitored carefully. *Gastrointestinal haemorrhage:* Gastrointestinal and intra-tumoural haemorrhages have been reported in patients with GIST. Gastric antral vascular ectasia (GAVE) has been reported in in patients with CML. *Tumour lysis syndrome (TLS):* Correct dehydration and treat high uric acid levels prior to treatment. *Hepatitis B (HBV)* reactivation: Reactivation of HBV has been reported and some cases resulted in acute hepatic complications, liver transplantation or a fatal outcome. Test for HBV before treatment initiation. Carriers of HBV should be closely monitored for HBV infection during therapy and after therapy for several months. *Phototoxicity:* Avoid or minimise exposure to direct sunlight. *Thrombotic Microangiopathy*: BCR-ABL tyrosine kinase inhibitors (TKIs) have been associated with thrombotic microangiopathy (TMA), including individual case reports for Glivec. If laboratory or clinical findings associated with TMA occur in a patient receiving Glivec, treatment should be discontinued and thorough evaluation for TMA, including ADAMTS13 activity and anti-ADAMTS13-antibody determination, should be completed. If anti-ADAMTS13-antibody is elevated in conjunction with low ADAMTS13 activity, treatment with Glivec should not be resumed. *Laboratory tests*: Complete blood counts must be performed regularly during treatment. Liver and renal function should be monitored regularly. Patients with severe renal impairment should be treated with caution. Long-term treatment with imatinib may be associated with a clinically significant decline in renal function. Caution should be recommended when driving a car or operating machinery.
Interactions: Use caution administering imatinib with CYP3A4 inhibitors (eg.protease inhibitors, azole antifungals, and certain macrolides). Concomitant use of imatinib and CYP3A4 inducers (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or St. John's Wort) may significantly reduce exposure to imatinib. Patients who require anticoagulation should receive low-molecular-weight or standard heparin, instead of coumarin derivatives such as warfarin. Caution is advised for CYP2D6 substrates with a narrow therapeutic window such as metoprolol. Exercise caution when using high doses of Glivec and paracetamol concomitantly.
Fertility, pregnancy and lactation: Use effective contraception. Do not use during pregnancy unless clearly necessary. If it is used during pregnancy, the patient must be informed of the potential risk to the foetus. Women taking imatinib should not breast-feed.
Undesirable effects: *Very common (≥1/10)*: neutropenia, thrombocytopenia, anaemia, headache, nausea, diarrhoea, vomiting, dyspepsia, abdominal pain, periorbital oedema, dermatitis/eczema/rash, muscle spasm and cramps, musculoskeletal pain including myalgia, arthralgia, bone pain, fluid retention and oedema, fatigue, weight increased. *Common (≥1/100 to <1/10)*: pancytopenia, febrile neutropenia, anorexia, insomnia, dizziness, paraesthesia, taste disturbance, hypoaesthesia, eyelid oedema, lacrimation increased, conjunctival haemorrhage, conjunctivitis, dry eye, blurred vision, flushing, haemorrhage, dyspnoea, epistaxis, cough, flatulence, abdominal distension, gastro-oesophageal reflux, constipation, dry mouth, gastritis, increased hepatic enzymes, pruritus, face oedema, dry skin, erythema, alopecia, night sweats, photosensitivity reaction, joint swelling, weakness, pyrexia, anasarca, chills, rigors, weight decreased.
Uncommon (≥1/1,000 to <1/100): herpes zoster, herpes simplex, pneumonia, sinusitis, cellulitis, upper respiratory tract infection, urinary tract infection, gastroenteritis, sepsis, thrombocythaemia, lymphopenia, bone marrow depression, eosinophilia, lymphadenopathy, hypokalaemia, hypophosphataemia, hyperuricaemia, hypercalcaemia, hyperglycaemia, hyponatraemia, depression, syncope, peripheral neuropathy, cerebral haemorrhage, orbital oedema, scleral haemorrhage, retinal haemorrhage, macular oedema, hearing loss, palpitations, tachycardia, cardiac failure congestive, pulmonary oedema, hypertension, haematoma, subdural haematoma, hypotension, pleural effusion, pharyngitis, stomatitis, gastrointestinal haemorrhage, melaena, oesophagitis, ascites, gastric ulcer, haematemesis, pancreatitis, hyperbilirubinaemia, hepatitis, jaundice, skin hypopigmentation, dermatitis exfoliative, purpura, renal failure acute, scrotal oedema, chest pain, blood creatinine increased, blood creatine phosphokinase increased, blood lactate dehydrogenase increased, blood alkaline phosphatase increased. *Rare (≥1/10,000 to <1/1,000)*: fungal infection, tumour lysis syndrome, haemolytic anaemia, thrombotic microangiopathy, hyperkalaemia, hypomagnesaemia, increased intracranial pressure, convulsions, optic neuritis, cataract, papilloedema, arrhythmia, atrial fibrillation, cardiac arrest, myocardial infarction, angina pectoris, pericardial effusion, pulmonary fibrosis, pulmonary hypertension, pulmonary haemorrhage, colitis, ileus, inflammatory bowel disease, hepatic failure, hepatic necrosis, acute febrile neutrophilic dermatosis, angioneurotic oedema, erythema multiforme, leucocytoclastic vasculitis, Stevens-Johnson syndrome, acute generalised exanthematous pustulosis, arthritis, rhabdomyolysis/myopathy, haemorrhagic corpus luteum/haemorrhagic ovarian cyst, blood amylase increased. *Not known*: HBV reactivation, tumour haemorrhage/tumour necrosis, anaphylactic shock, cerebral oedema, vitreous haemorrhage, pericarditis, cardiac tamponade, thrombosis/embolism, acute respiratory failure, interstitial lung disease, ileus/intestinal obstruction, gastrointestinal perforation, diverticulitis, GAVE, palmoplantar erythrodysesthesia syndrome, lichenoid keratosis, lichen planus, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms, pseudoporphyria, avascular necrosis/hip necrosis, growth retardation in children, renal failure chronic.
Other Adverse Effects: Please consult the Summary of Product Characteristics for a detailed listing of all adverse events before prescribing.
Legal classification: POM.
Marketing Authorisation number, quantities and NHS price:
EU/1/01/198/008 – 100mg x 60 tablets, £973.32
EU/1/01/198/010 – 400mg x 30 tablets, £1,946.67
Date of last revision of prescribing information: **April 2019. ONC19-C028**
Full Prescribing Information available from: Novartis Pharmaceuticals UK Ltd, Frimley Business Park, Frimley, Camberley, Surrey, GU16 7SR. Tel: 01276 692255, Fax: 01276 692508.

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