▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 of the SmPC for how to report adverse reactions.

Bosulif® ▼ (bosutinib) Prescribing Information:
Please refer to the Summary of Product Characteristics (SmPC) before prescribing Bosulif 100mg, 400mg or 500mg film-coated tablets.
Presentation: Film-coated tablet containing 100mg, 400mg or 500mg bosutinib (as monohydrate).
Indications: Bosutinib is indicated for the treatment of adult patients with newly diagnosed chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML), or CP, accelerated phase (AP), and blast phase (BP) Ph+ CML previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options. **Dosage:** Therapy should be initiated by a physician experienced in the diagnosis and the treatment of patients with CML. *Newly-diagnosed CP Ph+ CML:* The recommended dose is 400 mg bosutinib daily with food. *CP, AP or BP Ph+ CML with resistance or intolerance to prior therapy:* The recommended dose of bosutinib is 500mg taken orally once daily with food. In clinical trials, treatment with bosutinib continued until disease progression or intolerance to therapy. In the Phase 1/2 clinical study in patients with CML who were resistant or intolerant to prior therapy, dose escalations from 500 mg to 600 mg once daily with food were allowed in patients who failed to demonstrate complete haematological response (CHR) by Week 8 or complete cytogenetic response (CCyR) by Week 12 and did not have Grade 3 or higher adverse events possibly-related to the investigational product. Whereas, in the Phase 3 study in patients with newly diagnosed CP CML treated with bosutinib 400 mg, dose escalations by 100 mg increments to a maximum of 600 mg once daily with food were permitted if the patient failed to demonstrate breakpoint cluster region-Abelson (BCR ABL) transcripts ≤ 10% at Month 3, did not have a Grade 3 or 4 adverse reaction at the time of escalation, and all Grade 2 non-haematological toxicities were resolved to at least Grade 1. For details of dose escalation and dose reduction guidelines for non-haematologic adverse reactions and for haematologic adverse reactions, refer to SmPC section 4.2. Patients with serum creatinine >1.5 x ULN were excluded from CML studies. Increasing exposure (area under curve [AUC]) in patients with moderate and severe renal impairment during studies was observed. For details of dosage in patients with moderate and severe renal impairment please refer to SmPC section 4.2. Caution should be exercised in patients with relevant cardiac disorders and in patients with recent or ongoing clinically significant gastrointestinal disorder (see section 4.4 of SmPC). No specific dose recommendation is necessary in the elderly (≥65 years). Since there is limited information in the elderly, caution should be exercised in these patients. The safety and efficacy of bosutinib in patients under 18 years of age has not been established. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Hepatic impairment. **Special warnings and precautions for use:** Treatment with bosutinib is associated with elevations in serum transaminases (ALT, AST). Transaminase elevations generally occurred early in the course of treatment. Patients receiving bosutinib should have liver function tests prior to treatment initiation and monthly for the first 3 months of treatment, and as clinically indicated. Treatment with bosutinib is associated with diarrhoea and vomiting, therefore patients with recent or ongoing clinically significant gastrointestinal disorder should use this medicinal product with caution and only after a careful benefit-risk assessment. Patients with diarrhoea and vomiting should be managed using standard-of-care treatment, including an antidiarrhoeal or antiemetic medicinal product and/or fluid replacement. In addition, diarrhoea and vomiting can also be managed by withholding bosutinib temporarily, dose reduction, and/or discontinuation of bosutinib (see SmPC sections 4.2 and 4.8). The antiemetic agent, domperidone, has the potential to increase QT interval prolongation and to induce "torsade de pointes"- arrhythmias; therefore, co-administration with domperidone should be avoided. It should only be used if other medicinal products are not efficacious. In these situations an individual benefit-risk assessment is mandatory and patients should be monitored for occurrence of QT prolongation. Treatment with bosutinib is associated with myelosuppression, defined as anaemia, neutropenia, and thrombocytopenia. Complete blood counts should be performed weekly for the first month and then monthly thereafter, or as clinically indicated. Treatment with bosutinib may be associated with fluid retention including pericardial effusion, pleural effusion, pulmonary oedema and/or peripheral oedema. Patients should be monitored and managed using standard-of-care treatment. Elevation in serum lipase has been observed. Caution is recommended in patients with previous history of pancreatitis. Bosutinib may predispose patients to bacterial, fungal, viral or protozoan infections. Automated machine-read QTc prolongation without accompanying arrhythmia has been observed. Bosutinib should be administered with caution to patients who have a history of or predisposition for QTc prolongation, who have uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia, or who are taking medicinal products that are known to prolong the QT interval. Monitoring for an effect on the QTc interval is advisable and a baseline ECG is recommended prior to initiating therapy with Bosutinib and as clinically indicated. Hypokalaemia or hypomagnesaemia must be corrected prior to bosutinib administration and should be monitored periodically during therapy. Treatment with bosutinib may result in a clinically significant decline in renal function in CML patients. A decline over time in estimated glomerular filtration rate (eGFR) has been observed in patients treated with bosutinib in clinical studies. It is important that renal function is assessed prior to treatment initiation and closely monitored during therapy with bosutinib, with particular attention in those patients who have pre-existing renal compromise or in those patients exhibiting risk factors for renal dysfunction, including concomitant use of medicinal products with potential for nephrotoxicity, such as diuretics, ACE inhibitors, angiotensin receptor blockers and nonsteroidal anti-inflammatory drugs (NSAIDs). According to population pharmacokinetic analyses, Asians had a lower clearance resulting in increased exposure. Therefore, these patients should be closely monitored for adverse reactions especially in case of dose escalation. Bosutinib can induce severe skin reactions such as Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. Bosutinib should be permanently discontinued in patients who experience a severe skin reaction during treatment. Due to the possible occurrence of tumour lysis syndrome (TLS), correction of clinically significant dehydration and treatment of high uric acid levels are recommended prior to initiation of bosutinib (see SmPC section 4.8). Reactivation of hepatitis B (HBV) in patients who are chronic carriers of this virus has occurred after these patients received BCR-ABL tyrosine kinase inhibitors. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome. Patients should be tested for HBV infection before initiating treatment with Bosulif. Experts in liver disease and in the treatment of hepatitis B should be consulted before treatment is initiated in patients with positive hepatitis B serology (including those with active disease) and for patients who test positive for HBV infection during treatment. Carriers of HBV who require treatment with Bosulif should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. Exposure to direct sunlight UV radiation should be avoided or minimised due to the risk of photosensitivity associated with bosutinib treatment. Patients should be instructed to use measures such as protective clothing and sunscreen with high SPF. The concomitant use of bosutinib with strong or moderate CYP3A inhibitors/inducers should be avoided as an increase/decrease in bosutinib plasma concentration will occur. Grapefruit products, including grapefruit juice and other foods that are known to inhibit CYP3A should be avoided. **Drug interactions:** The concomitant use of bosutinib with strong CYP3A inhibitors (including, but not limited to itraconazole, ketoconazole, posaconazole, voriconazole, clarithromycin, telithromycin, nefazodone, mibefradil, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir, boceprevir, telaprevir, grapefruit products including grapefruit juice) or moderate CYP3A inhibitors (including, but not limited to fluconazole, ciprofloxacin, erythromycin, diltiazem, verapamil, amprenavir, atazanavir, darunavir/ritonavir, fosamprenavir, aprepitant, crizotinib, imatinib) should be avoided, as an increase in bosutinib plasma concentration will occur. Refer to section 4.5 of the SmPC for further details. If a strong or moderate CYP3A inhibitor must be administered during bosutinib treatment, an interruption of bosutinib therapy or a dose reduction in bosutinib should be considered. The concomitant use of bosutinib with strong CYP3A inducers (including, but not limited to carbamazepine, phenytoin, rifampicin, St. John's Wort), or moderate CYP3A inducers (including, but not limited to bosentan, efavirenz, etravirine, modafinil, nafcillin) should be avoided, as a decrease in bosutinib plasma concentration will occur. Caution should be exercised when administering bosutinib concomitantly with proton pump inhibitors (PPIs). Short-acting antacids should be considered as an alternative to PPIs and administration times of bosutinib and antacids should be separated (i.e. take bosutinib in the morning and antacids in the evening) whenever possible. Bosutinib should be used with caution in patients who have or may develop prolongation of QT, including those patients taking anti-arrhythmic medicinal products or other medicinal products that may lead to QT prolongation. Refer to sections 4.4 and 4.5 of the SmPC for further details. **Fertility, pregnancy and lactation:** Not recommended in pregnancy or whilst breast feeding. Bosutinib has the potential to impair reproductive function and fertility. Men being treated with bosutinib are advised to seek advice on conservation of sperm prior to treatment because of the possibility of decreased fertility due to therapy with bosutinib **Driving and operating machinery:** Bosutinib has no or negligible influence on the ability to drive and use machines. **Undesirable effects:** Very common adverse events are: respiratory tract infection(including lower respiratory tract infection, respiratory tract infection viral, upper respiratory tract infection, viral upper respiratory tract infection, nasopharyngitis, thrombocytopenia (including platelet count decreased), neutropenia (including neutrophil count decreased), anaemia (including haemoglobin decreased), decreased appetite, headache, dyspnoea, cough, diarrhoea, vomiting, nausea, abdominal pain (including abdominal discomfort, abdominal pain lower, abdominal pain upper, abdominal tenderness, gastrointestinal pain), alanine aminotransferase increased, aspartate aminotransferase increased, rash (including rash generalised, rash macular, rash maculo papular, rash papular, rash pruritic), arthralgia, back pain, pyrexia, asthenia, oedema (including face oedema, localised oedema, oedema peripheral), fatigue (including malaise), lipase increased (including hyperlipasaemia). Commonly reported adverse events are: pneumonia (including atypical pneumonia), influenza, bronchitis, leukopenia (including white blood cell count decreased), dehydration, hyperkalaemia, hypophosphataemia, dizziness, dysgeusia, tinnitus, pericardial effusion, electrocardiogram QT prolonged (including long QTc syndrome), hypertension (including blood pressure increased, blood pressure systolic increased, essential hypertension, hypertensive crisis), pleural effusion, gastritis, gastrointestinal haemorrhage (including anal haemorrhage, gastric haemorrhage, intestinal haemorrhage, lower gastrointestinal haemorrhage, rectal haemorrhage), hepatotoxicity (including hepatitis, hepatitis toxic, liver disorder), hepatic function abnormal (including liver function test abnormal, liver function test increased, transaminases increased), blood bilirubin increased (including hyperbilirubinaemia), gamma glutamyltransferase increased, urticaria, acne, pruritus, photosensitivity reaction, myalgia, acute kidney injury, renal failure, renal impairment, chest pain (including chest discomfort), pain, blood creatinine increased, amylase increased, blood creatine phosphokinase increased. Refer to section 4.8 of the SmPC for further information on side effects, including description of selected adverse reactions. **Legal category:** POM. **Basic NHS price:** Bosulif 100mg, 28 tablets [EU/1/13/818/001] £859.17. Bosulif 400 mg, 28 tablets [EU/1/13/818/006] £3436.67. Bosulif 500 mg, 28 tablets [EU/1/13/818/003] £3436.67. **Marketing authorisation holder:** Pfizer Europe MA EEIG, Boulevard de la Plaine 17, 1050 Bruxelles, Belgium.

Further information is available on request from: Medical Information at Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey, KT20 7NS, UK. Tel: +44 (0) 1304 616161

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Pfizer Medical Information on 01304 616161.

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