ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼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 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Bosulif 100 mg film-coated tablets
Bosulif 500 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Bosulif 100 mg film-coated tablets
Each film-coated tablet contains 100 mg bosutinib (as monohydrate).

Bosulif 500 mg film-coated tablets
Each film-coated tablet contains 500 mg bosutinib (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Bosulif 100 mg film-coated tablets
Yellow oval biconvex, film-coated tablet debossed with “Pfizer” on one side and “100” on the other side.

Bosulif 500 mg film-coated tablets
Red oval biconvex, film-coated tablet debossed with “Pfizer” on one side and “500”on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Bosulif is indicated for the treatment of adult patients with:

- newly-diagnosed chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML).
- CP, accelerated phase (AP), and blast phase (BP) Ph+ CML previously treated with one or more tyrosine kinase inhibitor(s) [TKI(s)] and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the diagnosis and the treatment of patients with CML.

Posology

Newly-diagnosed CP Ph+ CML
The recommended dose is 400 mg bosutinib once daily.

CP, AP, or BP Ph+ CML with resistance or intolerance to prior therapy
The recommended dose is 500 mg bosutinib once daily.

In clinical trials for both indications, treatment with bosutinib continued until disease progression or intolerance to therapy.

Dose adjustments
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.

In the Phase 1/2 clinical study in patients with CML who were resistant or intolerant to prior therapy who started treatment at ≤ 500 mg, 93 (93/558; 16.7%) patients had dose escalations to 600 mg daily.

In the Phase 3 study in patients with newly-diagnosed CP CML who started bosutinib treatment at 400 mg, a total of 46 patients (17.2%) received dose escalations to 500 mg. In addition, 5.6% of patients in the bosutinib treatment group had further dose escalations to 600 mg.

Doses greater than 600 mg/day have not been studied and, therefore, should not be given.

Dose adjustments for adverse reactions

Non-haematological adverse reactions
If clinically significant moderate or severe non-haematological toxicity develops, bosutinib should be interrupted, and may be resumed at a dose reduced by 100 mg taken once daily after the toxicity has resolved. If clinically appropriate, re-escalation to the dose prior to the dose reduction taken once daily should be considered (see section 4.4). Doses less than 300 mg/day have been used in patients; however, efficacy has not been established.

Elevated liver transaminases: If elevations in liver transaminases > 5 × institutional upper limit of normal (ULN) occur, bosutinib should be interrupted until recovery to ≤ 2.5 × ULN and may be resumed at 400 mg once daily thereafter. If recovery takes longer than 4 weeks, discontinuation of bosutinib should be considered. If transaminase elevations ≥ 3 × ULN occur concurrently with bilirubin elevations > 2 × ULN and alkaline phosphatase < 2 × ULN, bosutinib should be discontinued (see section 4.4).

Diarrhoea: For NCI Common Terminology Criteria for Adverse Events (CTCAE) Grade 3-4 diarrhoea, bosutinib should be interrupted and may be resumed at 400 mg once daily upon recovery to grade ≤ 1 (see section 4.4).

Haematological adverse reactions
Dose reductions are recommended for severe or persistent neutropenia and thrombocytopenia as described in Table 1:

Table 1 – Dose adjustments for neutropenia and thrombocytopenia

ANC[a] < 1.0×10^9/L and/or Platelets < 50×10^9/L	Hold bosutinib until ANC ≥ 1.0×10^9/L and platelets ≥ 50×10^9/L. Resume treatment with bosutinib at the same dose if recovery occurs within 2 weeks. If blood counts remain low for > 2 weeks, upon recovery reduce dose by 100 mg and resume treatment. If cytopoenia recurs, reduce dose by an additional 100 mg upon recovery and resume treatment. Doses less than 300 mg/day have been used; however, efficacy has not been established.

[a] ANC = absolute neutrophil count

<u>*Special populations*</u>

Elderly patients (≥ 65 years)
No specific dose recommendation is necessary in the elderly. Since there is limited information in the elderly, caution should be exercised in these patients.

Renal impairment
Patients with serum creatinine > 1.5×ULN were excluded from CML studies. Increasing exposure (area under curve [AUC]) in patients with moderate and severe renal impairment during studies was observed.

Newly-diagnosed CP Ph+ CML
In patients with moderate renal impairment (creatinine clearance [CL_{Cr}] 30 to 50 mL/min, estimated by the Cockcroft-Gault formula), the recommended dose of bosutinib is 300 mg daily with food (see sections 4.4 and 5.2).

In patients with severe renal impairment (CL_{Cr} < 30 mL/min, estimated by the Cockcroft-Gault formula), the recommended dose of bosutinib is 200 mg daily with food (see sections 4.4 and 5.2).

Dose escalation to 400 mg once daily with food for patients with moderate renal impairment or to 300 mg once daily for patients with severe renal impairment may be considered if they do not experience severe or persistent moderate adverse reactions and if they do not achieve an adequate haematological, cytogenetic, or molecular response.

CP, AP, or BP Ph+ CML with resistance or intolerance to prior therapy
In patients with moderate renal impairment (CL_{Cr} 30 to 50 mL/min, calculated by the Cockcroft-Gault formula), the recommended dose of bosutinib is 400 mg daily (see sections 4.4 and 5.2).

In patients with severe renal impairment (CL_{Cr} < 30 mL/min, calculated by the Cockcroft-Gault formula), the recommended dose of bosutinib is 300 mg daily (see sections 4.4 and 5.2).

Dose escalation to 500 mg once daily for patients with moderate renal impairment or to 400 mg once daily in patients with severe renal impairment may be considered in those who did not experience severe or persistent moderate adverse reactions, and if they do not achieve an adequate haematological, cytogenetic, or molecular response.

Cardiac disorders
In clinical studies, patients with uncontrolled or significant cardiac disease (e.g., recent myocardial infarction, congestive heart failure or unstable angina) were excluded. Caution should be exercised in patients with relevant cardiac disorders (see section 4.4).

Recent or ongoing clinically significant gastrointestinal disorder
In clinical studies, patients with recent or ongoing clinically significant gastrointestinal disorder (e.g., severe vomiting and/or diarrhoea) were excluded. Caution should be exercised in patients with recent or ongoing clinically significant gastrointestinal disorder (see section 4.4).

Paediatric population
The safety and efficacy of bosutinib in children less than 18 years of age have not been established. No data are available.

Method of administration
Bosulif should be taken orally once daily with food (see section 5.2). If a dose is missed by more than 12 hours, the patient should not be given an additional dose. The patient should take the usual prescribed dose on the following day.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hepatic impairment (see sections 5.1 and 5.2).

4.4 Special warnings and precautions for use

Liver function abnormalities
Treatment with bosutinib is associated with elevations in serum transaminases (alanine aminotransferase [ALT], aspartate aminotransferase [AST]).

Transaminase elevations generally occurred early in the course of treatment (of the patients who experienced transaminase elevations of any grade, > 80% experienced their first event within the first 3 months). 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.

Patients with transaminase elevations should be managed by withholding bosutinib temporarily (with consideration given to dose reduction after recovery to Grade 1 or baseline), and/or discontinuation of bosutinib. Elevations of transaminases, particularly in the setting of concomitant increases in bilirubin, may be an early indication of drug-induced liver injury and these patients should be managed appropriately (see sections 4.2 and 4.8).

Diarrhoea and vomiting
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 as respective patients were excluded from the clinical studies. 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, these events can also be managed by withholding bosutinib temporarily, dose reduction, and/or discontinuation of bosutinib (see sections 4.2 and 4.8). The antiemetic agent, domperidone, has the potential to increase QT interval (QTc) 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 QTc prolongation.

Myelosuppression
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. Myelosuppression should/can be managed by withholding bosutinib temporarily, dose reduction, and/or discontinuation of bosutinib (see sections 4.2 and 4.8).

Fluid retention
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. In addition, these events can also be managed by withholding bosutinib temporarily, dose reduction, and/or discontinuation of bosutinib (see sections 4.2 and 4.8).

Serum lipase
Elevation in serum lipase has been observed. Caution is recommended in patients with previous history of pancreatitis. In case lipase elevations are accompanied by abdominal symptoms, bosutinib should be interrupted and appropriate diagnostic measures considered to exclude pancreatitis (see section 4.2).

Infections
Bosutinib may predispose patients to bacterial, fungal, viral, or protozoan infections.

Proarrhythmic potential
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 QTc (e.g., anti-arrhythmic medicinal products and other substances that may prolong QTc [see section 4.5]). The presence of hypokalaemia and hypomagnesaemia may further enhance this effect.

Monitoring for an effect on the QTc is advisable and a baseline electrocardiogram (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.

Renal impairment
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. In patients with newly-diagnosed CP CML treated with 400 mg, the median decline from baseline in eGFR was 4.9 ml/min/1.73 m^2 at 3 months, 9.2 ml/min/1.73 m^2 at 6 months and 11.1 ml/min/1.73 m^2 at 12 months. Treatment-naïve CML patients treated with 500 mg showed a median eGFR decline of 5.1 ml/min/1.73 m^2 at 3 months, of 9.2 ml/min/1.73 m^2 at 12 months and of up to 16.3 ml/min/1.73 m^2 until 5 years follow-up for patients on treatment. Pretreated and advanced stage CML patients on 500 mg showed a median eGFR decline of 5.3 ml/min/1.73 m^2 at 3 months, of 7.6 ml/min/1.73 m^2 at 12 months and of up to 10.9 ml/min/1.73 m^2 in up to 4 years on treatment.. 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, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and nonsteroidal anti-inflammatory drugs (NSAIDs).

In a renal impairment study, bosutinib exposures were increased in subjects with moderately and severely impaired renal function. Dose reduction is recommended for patients with moderate or severe renal impairment (see sections 4.2 and 5.2).

Patients with serum creatinine > 1.5 × ULN were excluded from the CML studies. Based on a population pharmacokinetic analysis increasing exposure (AUC) in patients with moderate and severe renal impairment at initiation of treatment during studies was observed (see sections 4.2 and 5.2).

Clinical data are very limited (n = 3) for CML patients with moderate renal impairment receiving an escalated dose of 600 mg bosutinib.

Severe skin reactions
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.

Tumour lysis syndrome
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 section 4.8).

Hepatitis B reactivation
Reactivation of hepatitis B (HBV) in patients who are chronic carriers of this virus has occurred after these patients received BCR-ABL TKIs. 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 bosutinib. Experts in liver disease and in the treatment of HBV should be consulted before treatment is initiated in patients with positive HBV serology (including those with active disease) and for patients who test positive for HBV infection during treatment. Carriers of HBV who require treatment with bosutinib should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy (see section 4.8).

Cytochrome P-450 (CYP)3A inhibitors
The concomitant use of bosutinib with strong or moderate CYP3A inhibitors should be avoided, as an increase in bosutinib plasma concentration will occur (see section 4.5).

Selection of an alternate concomitant medicinal product with no or minimal CYP3A inhibition potential, if possible, is recommended.

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.

CYP3A inducers
The concomitant use of bosutinib with strong or moderate CYP3A inducers should be avoided as a decrease in bosutinib plasma concentration will occur (see section 4.5).

Food effect
Grapefruit products, including grapefruit juice and other foods that are known to inhibit CYP3A should be avoided (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on bosutinib

CYP3A inhibitors
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.

Caution should be exercised if mild CYP3A inhibitors are used concomitantly with bosutinib.

Selection of an alternate concomitant medicinal product with no or minimal CYP3A enzyme inhibition potential, if possible, is recommended.

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.

In a study of 24 healthy subjects in whom 5 daily doses of 400 mg ketoconazole (a strong CYP3A inhibitor) were co-administered with a single dose of 100 mg bosutinib under fasting conditions, ketoconazole increased bosutinib C_{max} by 5.2-fold, and bosutinib AUC in plasma by 8.6-fold, as compared with administration of bosutinib alone.

In a study of 20 healthy subjects, in whom a single dose of 125 mg aprepitant (a moderate CYP3A inhibitor) was co-administered with a single dose of 500 mg bosutinib under fed conditions, aprepitant increased bosutinib C_{max} by 1.5-fold, and bosutinib AUC in plasma by 2.0-fold, as compared with administration of bosutinib alone.

CYP3A inducers
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.

Based on the large reduction in bosutinib exposure that occurred when bosutinib was co-administered with rifampicin, increasing the dose of bosutinib when co-administering with strong or moderate CYP3A inducers is unlikely to sufficiently compensate for the loss of exposure.

Caution is warranted if mild CYP3A inducers are used concomitantly with bosutinib.

Following concomitant administration of a single dose bosutinib with 6 daily doses of 600 mg rifampicin, in 24 healthy subjects in fed state bosutinib exposure (C_{max} and AUC in plasma) decreased to 14% and 6%, respectively, of the values when bosutinib 500 mg was administered alone.

Proton pump inhibitors (PPIs)
Caution should be exercised when administering bosutinib concomitantly with 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 displays pH-dependent aqueous solubility *in vitro*. When a single oral dose of bosutinib (400 mg) was co-administered with multiple-oral doses of lansoprazole (60 mg) in a study of 24 healthy fasting subjects, bosutinib C_{max} and AUC decreased to 54% and 74%, respectively, of the values seen when bosutinib (400 mg) was given alone.

Effects of bosutinib on other medicinal products
In a study of 27 healthy subjects, in whom a single dose of 500 mg bosutinib was co-administered with a single dose of 150 mg dabigatran etexilate mesylate (a P-glycoprotein [P-gp] substrate) under fed conditions, bosutinib did not increase C_{max} or AUC of dabigatran in plasma, as compared with administration of dabigatran etexilate mesylate alone. The study results indicate that bosutinib does not exhibit clinically relevant P-gp inhibitory effects.

An *in vitro* study indicates that drug-drug interactions are unlikely to occur at therapeutic doses as a result of induction by bosutinib on the metabolism of medicinal products that are substrates for CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A4.

In vitro studies indicate that clinical drug-drug interactions are unlikely to occur at therapeutic doses as a result of inhibition by bosutinib on the metabolism of medicinal products that are substrates for CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5.

In vitro studies indicate that bosutinib has a low potential to inhibit breast cancer resistance protein (BCRP, systemically), organic anion transporting polypeptide (OATP)1B1, OATP1B3, organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2 at clinically relevant concentrations, but may have the potential to inhibit BCRP in the gastrointestinal tract and OCT1.

Anti-arrhythmic medicinal products and other substances that may prolong QT
Bosutinib should be used with caution in patients who have or may develop prolongation of QT, including those 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, domperidone, haloperidol, methadone, and moxifloxacin (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential should be advised to use effective contraception and avoid becoming pregnant while receiving bosutinib. In addition, the patient should be advised that vomiting or diarrhoea may reduce the efficacy of oral contraceptives by preventing full absorption.

Pregnancy
There are limited amount of data in pregnant women from the use of bosutinib. Studies in animals have shown reproductive toxicity (see section 5.3). Bosutinib is not recommended for use during pregnancy, or in women of childbearing potential not using contraception. If bosutinib is used during pregnancy, or the patient becomes pregnant while taking bosutinib, she should be apprised of the potential hazard to the foetus.

Breast-feeding
It is unknown whether bosutinib and its metabolites are excreted in human milk. A study of [^{14}C] radiolabelled bosutinib in rats demonstrated excretion of bosutinib-derived radioactivity in breast milk (see section 5.3). A potential risk to the breast-feeding infant cannot be excluded. Breast-feeding should be discontinued during treatment with bosutinib.

Fertility
Based on non-clinical findings, bosutinib has the potential to impair reproductive function and fertility in humans (see section 5.3). 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.

4.7 Effects on ability to drive and use machines

Bosutinib has no or negligible influence on the ability to drive and use machines. However, if a patient taking bosutinib experiences dizziness, fatigue, visual impairment or other undesirable effects with a potential impact on the ability to drive or use machines safely, the patient should refrain from these activities for as long as the undesirable effects persist.

4.8 Undesirable effects

Summary of safety profile

A total of 1,272 leukaemia patients received at least 1 dose of single-agent bosutinib. The median duration of therapy was 13.8 months (range: 0.03 to 123.3 months). These patients were either newly diagnosed, with CP CML or were resistant or intolerant to prior therapy with chronic, accelerated, or blast phase CML or Ph+ acute lymphoblastic leukaemia (ALL). Of these patients, 268 (400 mg starting dose) and 248 (500 mg starting dose) are from the 2 Phase 3 studies in previously untreated CML patients, 570 and 63 are from 2 Phase 1/2 studies in previously treated Ph+ leukaemias, and 123 patients from a Phase 4 study in previously treated CML. The median duration of therapy was 14.1 months (range: 0.3 to 24.7 months), 61.6 months (0.03 to 99.6 months), 11.1 months (range: 0.03 to 123.3 months), 30.2 months (range: 0.3 to 85.6 months), and 5.7 months (range: 0.07 to 17.8 months), respectively. The safety analyses included data from an ongoing extension study.

At least 1 adverse reaction of any toxicity grade was reported for 1,240 (97.5%) patients. The most frequent adverse reactions reported for ≥ 20% of patients were diarrhoea (78.1%), nausea (40.8%), thrombocytopenia (34.9%), abdominal pain (34.0%), vomiting (33.0%), rash (31.5%), anaemia (25.6%), pyrexia (21.8%), fatigue (21.4%), and ALT increased (25.0%). At least 1 Grade 3 or Grade 4 adverse reaction was reported for 814 (63.9%) patients. The Grade 3 or Grade 4 adverse reactions reported for ≥ 5% of patients were thrombocytopenia (20.3%), anaemia (10.2%), neutropenia (10.5%), ALT increased (12.7%), diarrhoea (9.6%), rash (5.0%), lipase increased (8.2%), and AST increased (5.8%).

Tabulated list of adverse reactions

The following adverse reactions were reported in patients in bosutinib clinical studies (Table 2). These represent an evaluation of the adverse reaction data from 1,272 patients with either newly-diagnosed CP CML or with chronic, accelerated, or blast phase CML resistant or intolerant to prior therapy or Ph+ ALL who have received at least 1 dose of single-agent bosutinib. These adverse reactions are presented by system organ class and frequency. Frequency categories are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2 - Adverse reactions for bosutinib

Infections and infestations	
Very common	Respiratory tract infection (including Lower respiratory tract infection, Respiratory tract infection viral, Upper respiratory tract infection, Viral upper respiratory tract infection), Nasopharyngitis
Common	Pneumonia (including Atypical pneumonia), Influenza, Bronchitis
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Uncommon	Tumour lysis syndrome**
Blood and lymphatic system disorders	
Very common	Thrombocytopenia (including Platelet count decreased), Neutropenia (including Neutrophil count decreased), Anaemia (including haemoglobin decreased)
Common	Leukopenia (including White blood cell count decreased)

Uncommon	Febrile neutropenia, Granulocytopenia
Immune system disorders	
Uncommon	Anaphylactic shock, Hypersensitivity
Metabolism and nutrition disorders	
Very common	Decreased appetite
Common	Dehydration, Hyperkalaemia, Hypophosphataemia
Nervous system disorders	
Very common	Headache
Common	Dizziness, Dysgeusia
Ear and labyrinth disorders	
Common	Tinnitus
Cardiac disorders	
Common	Pericardial effusion, Electrocardiogram QTc prolonged (including Long QTc syndrome)
Uncommon	Pericarditis
Vascular disorders	
Common	Hypertension (including Blood pressure increased, Blood pressure systolic increased, Essential hypertension, Hypertensive crisis)
Respiratory, thoracic and mediastinal disorders	
Very common	Dyspnoea, Cough
Common	Pleural effusion
Uncommon	Pulmonary hypertension, Respiratory failure, Acute pulmonary oedema
Gastrointestinal disorders	
Very common	Diarrhoea, Vomiting, Nausea, Abdominal pain (including Abdominal discomfort, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness, Gastrointestinal pain)
Common	Gastritis, Gastrointestinal haemorrhage (including Anal haemorrhage, Gastric haemorrhage, Intestinal haemorrhage, Lower gastrointestinal haemorrhage, Rectal haemorrhage)
Uncommon	Pancreatitis (including Pancreatitis acute)
Hepatobiliary disorders	
Very common	Alanine aminotransferase increased, Aspartate aminotransferase increased
Common	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
Uncommon	Liver injury (including Drug-induced liver injury)
Skin and subcutaneous tissue disorders	
Very common	Rash (including Rash generalised, Rash macular, Rash maculo-papular, Rash papular, Rash pruritic)
Common	Urticaria, Acne, Pruritus
Uncommon	Exfoliative rash, Drug eruption
Rare	Erythema multiforme
Unknown	Stevens-Johnson Syndrome[**], Toxic epidermal necrolysis[**]
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia, Back pain
Common	Myalgia
Renal and urinary disorders	
Common	Acute kidney injury, Renal failure, Renal impairment
General disorders and administration site conditions	
Very common	Pyrexia, Asthenia, Oedema (including Face oedema, Localised oedema, Oedema peripheral), Fatigue (including Malaise)
Common	Chest pain (including Chest discomfort), Pain

Investigations	
Very common	Lipase increased (including Hyperlipasaemia)
Common	Blood creatinine increased, Amylase increased, Blood creatine phosphokinase increased

** Adverse reaction identified post marketing.

Description of selected adverse reactions

The descriptions included below are based on the safety population of 1,272 patients who received at least 1 dose of bosutinib for either newly-diagnosed CP CML or were resistant or intolerant to prior therapy with CP, AP, or BP CML, or Ph+ ALL.

Blood and lymphatic system disorders

Of the 297 (23%) patients with reports of adverse reactions of anaemia, 3 patients discontinued bosutinib due to anaemia. In these patients, the maximum toxicity of Grade 1 or 2 was experienced in 174 (58%) patients, Grade 3 in 96 patients (32%), and Grade 4 in 27 (9%) patients. Among these patients, the median time to first event was 28 days (range: 1 to 2,633 days) and the median duration per event was 15 days (range: 1 to 1,529 days).

Of the 197 (15%) patients with reports of adverse reactions of neutropenia, 15 patients discontinued bosutinib due to neutropenia. Maximum Grade 1 or 2 events were experienced by 63 (32%) patients. The maximum toxicity of Grade 3 neutropenia was experienced in 90 (46%) patients and of Grade 4 in 44 (22%) patients. The median time to first event was 59 days (range: 27 to 505 days), and the median duration per event was 15 days (range: 1 to 913 days).

Of the 445 (35%) patients with reports of adverse reactions of thrombocytopenia, 41 (9%) patients discontinued treatment with bosutinib due to thrombocytopenia. Maximum Grade 1 or 2 events were experienced by 186 (42%) patients. The maximum toxicity of thrombocytopenia of Grade 3 was experienced in 161 (36%) patients and Grade 4 in 98 (22%) patients. Among patients with thrombocytopenia adverse events, the median time to first event was 28 days (range: 1 to 1,688 days), and median duration per event was 15 days (range: 1 to 1,762 days).

Hepatobiliary disorders

Among patients with reports of adverse reactions of elevations in either ALT or AST (all grades), the median time of onset observed was 29 days with a range of onset 1 to 2,465 days for ALT and AST. The median duration of an event was 18 days (range: 1 to 775 days), and 15 days (range: 1 to 803 days) for ALT and AST, respectively.

In the entire development program, concurrent elevation in transaminases $\geq 3 \times$ ULN and bilirubin $> 2 \times$ ULN with alkaline phosphatase $< 2 \times$ ULN occurred without alternative causes in 1/1,611 (<0.1%) subjects treated with bosutinib. This finding was in a study of bosutinib in combination with letrozole in a patient with metastatic breast cancer.

Hepatitis B reactivation

Hepatitis B reactivation has been reported in association with BCR-ABL TKIs. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome (see section 4.4).

Gastrointestinal disorders

Of the 994 (78%) patients that experienced diarrhoea, 965 patients had drug-related events of diarrhoea and 10 patients discontinued bosutinib due to this event. Concomitant medicinal products were given to treat diarrhoea in 662 (66%) patients. The maximum toxicity of diarrhoea was Grade 1 or 2 in 88% of patients, Grade 3 in 12% of patients; 1 patient (< 1%) experienced a Grade 4 event. Among patients with diarrhoea, the median time to first event was 2 days (range: 1 to 2,415 days) and the median duration of any grade of diarrhoea was 2 days (range: 1 to 2,511 days).

Among the 994 patients with diarrhoea, 180 patients (18%) were managed with treatment interruption and of these 170 (94%) were rechallenged with bosutinib. Of those who were rechallenged, 167 (98%) did not have a subsequent event or did not discontinue bosutinib due to a subsequent event of diarrhoea.

Cardiac disorders
Four patients (0.3%) experienced QTcF interval prolongation (greater than 500 ms). Nine (0.8%) patients experienced QTcF increase from baseline exceeding 60 ms. Patients with uncontrolled or significant cardiovascular disease including QTc prolongation, at baseline, were not included in clinical studies (see sections 5.1 and 5.3).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Experience with bosutinib overdose in clinical studies was limited to isolated cases. Patients who take an overdose of bosutinib should be observed and given appropriate supportive treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01XE14.

Mechanism of action
Bosutinib belongs to a pharmacological class of medicinal products known as kinase inhibitors. Bosutinib inhibits the abnormal BCR-ABL kinase that promotes CML. Modeling studies indicate that bosutinib binds the kinase domain of BCR-ABL. Bosutinib is also an inhibitor of Src family kinases including Src, Lyn and Hck. Bosutinib minimally inhibits platelet-derived growth factor (PDGF) receptor and c-Kit.

In *in vitro* studies, bosutinib inhibits proliferation and survival of established CML cell lines, Ph+ ALL cell lines, and patient-derived primary primitive CML cells. Bosutinib inhibited 16 of 18 imatinib-resistant forms of BCR-ABL expressed in murine myeloid cell lines. Bosutinib treatment reduced the size of CML tumours growing in nude mice and inhibited growth of murine myeloid tumours expressing imatinib-resistant forms of BCR-ABL. Bosutinib also inhibits receptor tyrosine kinases c-Fms, EphA and B receptors, Trk family kinases, Axl family kinases, Tec family kinases, some members of the ErbB family, the non-receptor tyrosine kinase Csk, serine/threonine kinases of the Ste20 family, and 2 calmodulin-dependent protein kinases.

Pharmacodynamic effects
The effect of bosutinib 500 mg administration on corrected QTc was evaluated in a randomised, single-dose, double-blind (with respect to bosutinib), crossover, placebo- and open-label moxifloxacin-controlled study in healthy subjects.

The data from this study indicate that bosutinib does not prolong the QTc in healthy subjects at the dose of 500 mg daily with food, and under conditions that give rise to supratherapeutic plasma concentrations. Following administration of a single oral dose of bosutinib 500 mg (therapeutic dose) and bosutinib 500 mg with ketoconazole 400 mg (to achieve supratherapeutic concentrations of bosutinib) in healthy subjects, the upper bound of the 1-sided 95% confidence interval (CI) around the

mean change in QTc was less than 10 ms at all post-dose time points, and no adverse events suggestive of QTc prolongation were observed.

In a study in liver impaired subjects, an increasing frequency of QTc prolongation > 450 ms with declining hepatic function was observed. In the Phase 1/2 clinical study in patients with previously treated Ph+ leukaemias, QTcF interval changes > 60 ms from baseline were observed in 6 (1.1%) of 562 patients. In the Phase 3 clinical study in patients with newly-diagnosed CP CML treated with bosutinib 400 mg, there were no patients in the bosutinib treatment group with an increase of > 60 ms from baseline when the QT interval was corrected using Fridericia's formula (QTcF). In the Phase 3 clinical study in patients with newly diagnosed Ph+ CP CML treated with bosutinib 500 mg, QTcF interval changes > 60 ms from baseline were observed in 2 (0.8%) of 248 patients receiving bosutinib. A proarrhythmic potential of bosutinib cannot be ruled out.

Clinical efficacy

Clinical study in CP previously untreated CML

Bosutinib 400 mg study
A 2-arm, Phase 3, open-label, multicentre superiority trial was conducted to investigate the efficacy and safety of bosutinib 400 mg once daily alone compared with imatinib 400 mg once daily alone in adult patients with newly-diagnosed Ph+ CP CML. The trial randomised 536 patients (268 in each treatment group) with Ph+ or Ph- newly-diagnosed CP CML (intent-to-treat population [ITT]) including 487 patients with Ph+ CML harbouring b2a2 and/or b3a2 transcripts and baseline BCR-ABL copies > 0 (modified intent-to-treat [mITT] population).

The primary efficacy endpoint was the proportion demonstrating a major molecular response (MMR) at 12 months (48 weeks) in the bosutinib treatment group compared with that in the imatinib treatment group in the mITT population. MMR was defined as ≤ 0.1% BCR-ABL/ABL ratio by international scale (corresponding to ≥ 3 log reduction from standardised baseline) with a minimum of 3,000 ABL transcripts as assessed by the central laboratory. The secondary efficacy endpoints included MMR by 18 months, duration of MMR, CCyR by 12 months, duration of CCyR, event-free survival (EFS), and overall survival (OS). Complete cytogenetic response by Month 12, a secondary endpoint, was defined as the absence of Ph+ metaphases in chromosome banding analysis of ≥ 20 metaphases derived from bone marrow aspirate or MMR if an adequate cytogenetic assessment was unavailable. The p-values for endpoints other than MMR at 12 months and CCyR by 12 months have not been adjusted for multiple comparisons.

Baseline characteristics for the mITT population were well balanced between the 2 treatment groups with respect to age (median age was52 years for the bosutinib group and 53 years for the imatinib group with 19.5% and 17.4% of patients 65 years of age or older, respectively); gender (women 42.3% and 44.0%, respectively); and race (Caucasian 77.6% and 77.2%, Asian 12.2% and 12.4%, Black or African American 4.1% and 4.1%, and Other 5.7% and 5.8%, respectively, and 1 unknown in each group).

After a minimum of 12 months of follow-up in the mITT population, 77.6% of patients treated with bosutinib (N=241) and 72.4% of patients treated with imatinib (N=239) were still receiving first-line treatment.

After a minimum of 12 months of follow-up in the mITT population, discontinuations due to disease progression to AP or BP CML for bosutinib-treated patients were 0.4% compared to 1.7% for imatinib-treated patients. Five bosutinib patients and 7 imatinib patients transformed to AP CML or BP CML. Discontinuations due to suboptimal response or treatment failure as assessed by the investigator occurred for 2.0% of patients in the bosutinib-treated group compared to 6.3% of patients in the imatinib-treated group. One patient on bosutinib and 7 patients on imatinib died while on study.

The efficacy results are summarised in Table 3.

Table 3 - Summary of MMR at Months 12 and 18 and CCyR by Month 12, by treatment group in the mITT population

Response	Bosutinib (N=246)	Imatinib (N=241)	1-sided p-value
Major molecular response (n, %)			
MMR at Month 12	116 (47.2)[a]	89 (36.9)	0.0100[a]
(95% CI)	(40.9, 53.4)	(30.8, 43.0)	
MMR at Month 18	140 (56.9)	115 (47.7)	0.0208[b]
(95% CI)	(50.7, 63.1)	(41.4, 54.0)	
Complete cytogenetic response by Month 12 (n, %)			
CCyR	190 (77.2)[a]	160 (66.4)	0.0037[a]
(95% CI)	(72.0, 82.5)	(60.4, 72.4)	

Note: MMR was defined as ≤ 0.1% BCR-ABL/ABL ratio by international scale (corresponding to ≥ 3 log reduction from standardised baseline) with a minimum of 3,000 ABL transcripts assessed by the central laboratory. Complete cytogenetic response was defined as the absence of Ph+ metaphases in chromosome banding analysis of ≥ 20 metaphases derived from bone marrow aspirate or MMR if an adequate cytogenetic assessment was unavailable.
Abbreviations: BCR-ABL=breakpoint cluster region-Abelson; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; CCyR=complete cytogenetic response; mITT=modified intent-to-treat; MMR=major molecular response; N/n=number of patients; Ph+=Philadelphia chromosome-positive.
[a] Statistically significant comparison at the pre-specified significance level; based on CMH test stratified by geographical region and Sokal score at randomisation.
[b] Based on CMH test stratified by geographical region and Sokal score at randomisation.

At Month 12, the MR[4] rate (defined as ≤ 0.01% BCR-ABL [corresponding to ≥ 4 log reduction from standardised baseline] with a minimum of 9,800 ABL transcripts) was higher in the bosutinib treatment group compared to the imatinib treatment group in the mITT population (20.7% [95% CI: 15.7%, 25.8%] versus 12.0% [95% CI: 7.9%, 16.1%], respectively, 1-sided p-value=0.0052).

At Months 3, 6, and 9, the proportion of patients with MMR was higher in the bosutinib treatment group compared to the imatinib treatment group (Table 4).

Table 4 - Comparison of MMR at Months 3, 6, and 9 by treatment in the mITT population

Time	Number (%) of subjects with MMR: Bosutinib (N=246)	Number (%) of subjects with MMR: Imatinib (N=241)	1-sided p-value[a]
Month 3	10 (4.1)	4 (1.7)	0.0578
(95% CI)	(1.6, 6.5)	(0.0, 3.3)	
Month 6	86 (35.0)	44 (18.3)	< 0.0001
(95% CI)	(29.0, 40.9)	(13.4. 23.1)	
Month 9	104 (42.3)	71 (29.5)	0.0015
(95% CI)	(36.1, 48.4)	(23.7, 35.2)	

Note: Percentages were based on number of patients in each treatment group. MMR was defined as ≤ 0.1% BCR-ABL/ABL ratio on international scale (corresponding to ≥ 3 log reduction from standardised baseline) with a minimum of 3,000 ABL transcripts assessed by the central laboratory.
Abbreviations: BCR-ABL=breakpoint cluster region-Abelson; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; CML=chronic myelogenous leukaemia; mITT=modified intent-to-treat; MMR=major molecular response; Ph+=Philadelphia chromosome-positive.
[a] p-value based on CMH test stratified by geographical region and Sokal score at randomisation.

The cumulative incidence of MMR adjusting for competing risk of treatment discontinuation without MMR was higher in the bosutinib treatment group compared to the imatinib treatment group in the mITT population (45.1% [95% CI: 38.8%, 51.2%] versus 33.7% [95% CI: 27.8%, 39.6%] at Week 48; hazard ratio [HR] from a stratified proportional subdistributional hazards model: 1.35 [95% CI: 1.07, 1.70], 1-sided p-value = 0.0086). The median time to MMR for responders was 24.7 weeks versus 36.3 weeks for the bosutinib treatment and imatinib treatment groups, respectively, in the mITT population.

The cumulative incidence of CCyR adjusted for the competing risk of treatment discontinuation without CCyR was higher in the bosutinib treatment group compared to the imatinib treatment group in the mITT population (79.1% [95% CI: 73.4%, 83.7%] versus 67.3% [95% CI: 60.9%, 72.8%] at Week 48; HR: 1.38, [95% CI: 1.13, 1.68]; 1-sided p-value=0.0003). The median time to CCyR (responders only) was 23.9 weeks in the bosutinib group compared to the 24.3 weeks imatinib group.

The Kaplan-Meier estimates of OS at 48 weeks for bosutinib and imatinib patients in the mITT population were 99.6% (95% CI: 97.1%, 99.9%) and 97.9% (95% CI: 95.0%, 99.1%), respectively.

No additional deaths or transformations occurred in the ITT population.

Clinical study in imatinib-resistant or intolerant CML in CP, AP, and BP
A single-arm, Phase 1/2 open-label, multicentre trial was conducted to evaluate the efficacy and safety of bosutinib 500 mg once daily in patients with imatinib-resistant or -intolerant CML with separate cohorts for chronic, accelerated, and blast phase disease previously treated with 1 prior TKI (imatinib) or more than 1 TKI (imatinib followed by dasatinib and/or nilotinib).

There were 570 patients treated with bosutinib in this trial including CP CML patients previously treated with only 1 prior TKI (imatinib), CP CML patients previously treated with imatinib and at least 1 additional TKI (dasatinib and/or nilotinib), CML patients in accelerated or blast phase previously treated with at least 1 TKI (imatinib) and patients with Ph+ ALL previously treated with at least 1 TKI (imatinib).

The primary efficacy endpoint of the study was the major cytogenetic response (MCyR) rate at Week 24 in patients with imatinib-resistant CP CML previously treated with only 1 prior TKI (imatinib). Other efficacy endpoints include the cumulative MCyR rate, time to and duration of MCyR, and time to and duration of CHR, in patients with CP CML previously treated with only 1 prior TKI (imatinib). For patients previously treated with both imatinib and at least 1 additional TKI, the endpoints include the cumulative MCyR rate, time to and duration of MCyR, and time to and duration of CHR. For patients with AP and BP CML previously treated with at least 1 prior TKI (imatinib), the endpoints were cumulative overall haematological response (OHR) and time to and duration of OHR. Other efficacy endpoints include transformation to AP/BP, progression free survival and OS for all cohorts.

CP
The efficacy results for Ph+ CP CML patients previously treated with imatinib and at least 1 additional TKI (minimum follow-up 48 months, median treatment duration of 9 months and 24.4% still on-treatment at 48 months) and the results for Ph+ CP CML patients previously treated with only imatinib (minimum follow-up 60 months, median treatment duration of 26 months and 40.5% still on-treatment at 60 months) are presented in Table 5.

AP and BP CML patients
The efficacy results for AP (minimum follow-up 48 months, median treatment duration of 10 months and 17.7% still on-treatment at 48 months) and BP (minimum follow-up 48 months, median treatment duration of 2.8 months and 3.1% still on-treatment at 48 months) Ph+ CML patients are present in Table 5.

Table 5 - Efficacy results in previously treated patients with chronic and advanced phase CML*

	Ph+ CP CML with prior imatinib treatment only	Ph+ CP CML with prior treatment with imatinib and dasatinib or nilotinib	Accelerated phase with prior treatment of at least imatinib	Blast phase with prior treatment of at least imatinib
Cumulative cytogenetic response[a]	N=262	N=112	N=72	N=54
MCyR, % (95% CI)	59.5 (53.3, 65.5)	40.2 (31.0, 49.9)	40.3 (28.9, 52.5)	37.0 (24.3, 51.3)
CCyR, % (95% CI)	49.6 (43.4, 55.8)	32.1 (23.6, 41.6)	30.6 (20.2, 42.5)	27.8 (16.5, 41.6)
Time to MCyR for responders only[b], weeks (95% CI)	12.3 (12.1, 12.7)	12.3 (12.0, 14.1)	12.0 (11.9, 12.1)	8.2 (4.3, 12.0)
Duration of MCyR[b]	N=156	N=45	N=29	N=20
K-M at year 1/2, % (95% CI)[c]	76.4 (68.5, 82.5)	72.0 (55.1, 83.4)	62.2 (41.1, 77.6)	21.2 (5.2, 44.2)
K-M at year 4/5, % (95% CI)[c]	71.1 (62.6, 78.0)	69.3 (52.3, 81.3)	46.7 (27.1, 64.1)	21.2 (5.2, 44.2)
Median , weeks (95% CI)	N/R	N/R	84.0 (24.0, N/E)	29.1 (11.9, 38.3)
Cumulative haematological response[d]	N=283	N=117	N=72	N=60
Overall, % (95% CI)	N/A	N/A	56.9 (44.7, 68.6)	28.3 (17.5, 41.4)
Major, % (95% CI)	N/A	N/A	47.2 (35.3, 59.3)	18.3 (9.5, 30.4)
Complete, % (95% CI)	86.6 (82.0, 90.3)	73.5 (64.5, 81.2)	33.3 (22.7, 45.4)	16.7 (8.3, 28.5)
Time to OHR for responders only, weeks (95% CI)	N/A	N/A	12.0 (11.1, 12.1)	8.9 (4.1, 12.0)
Duration of CHR/OHR[e]	N=245	N=86	N=41	N=17
K-M at year 1/2, % (95% CI)[c]	71.9 (65.1, 77.6)	73.4 (61.7, 82.1)	78.2 (59.4, 89.0)	28.4 (7.8, 53.9)
K-M at year 4/5, % (95% CI)[c]	66.0 (58.8, 72.3)	62.9 (50.1, 73.3)	52.0 (32.3, 68.5)	19.0 (3.3, 44.5)
Median, weeks (95% CI)	N/R	N/R	207.0 (63.1, N/E)	32.0 (29.0, 54.6)
Transformation to AP/BP[f]	N=284	N=119	N=79	N/A
On--treatment transformation, n	15	5	3	

	Ph+ CP CML with prior imatinib treatment only	Ph+ CP CML with prior treatment with imatinib and dasatinib or nilotinib	Accelerated phase with prior treatment of at least imatinib	Blast phase with prior treatment of at least imatinib
Progression-free survival[f]	N=284	N=119	N=79	N=64
K-M at year 1/2, % (95% CI)[c]	80.0 (73.9, 84.8)	75.1 (64.6, 82.9)	66.8 (53.4, 77.1)	16.1 (6.6, 29.3)
K-M at year 4/5, % (95% CI)[c]	72.5 (65.6, 78.2)	65.1 (53.1, 74.8)	40.8 (26.6, 54.5)	8.0 (1.7, 21.2)
Median, months (95% CI)	N/R	N/R	22.1 (14.6, N/E)	4.4 (3.2, 8.5)
Overall survival[f]	N=284	N=119	N=79	N=64
K-M at year 1/2, % (95% CI)[c]	91.2 (87.1, 94.0)	91.3 (84.5, 95.2)	78.1 (67.1, 85.8)	42.1 (29.7, 53.9)
K-M at year 4/5, % (95% CI)[c]	83.1 (77.5, 87.4)	77.0 (66.9, 84.4)	58.4 (45.6, 69.1)	20.1 (6.2, 39.8)
Median, months (95% CI)	N/R	N/R	N/R	10.9 (8.7,19.7)

* For efficacy results in the subgroup of patients corresponding to the approved indication, see text above.
Snapshot date: 02Oct2015
Cytogenetic Response criteria: Major Cytogenetic Response included Complete [0% Ph+ metaphases from bone marrow or < 1% positive cells from fluorescent in situ hybridisation (FISH)] or partial (1%-35%) cytogenetic responses. Cytogenetic responses were based on the percentage of Ph+ metaphases among ≥ 20 metaphase cells in each bone marrow sample. FISH analysis (≥ 200 cells) could be used for post-baseline cytogenetic assessments if ≥ 20 metaphases were not available.
Overall haematological response (OHR)=major haematological response (complete haematological response + no evidence of leukaemia) or return to chronic phase (RCP). All responses were confirmed after 4 weeks. Complete haematological response (CHR for AP and BP CML: WBC less than or equal to institutional upper limit of normal (ULN), platelets greater than or equal to 100,000/mm^3 and less than 450,000/mm^3, absolute neutrophil count (ANC) greater than or equal to 1.0×10^9/L, no blasts or promyelocytes in peripheral blood, less than 5% myelocytes + metamyelocytes in bone marrow, less than 20% basophils in peripheral blood, and no extramedullary involvement. No evidence of leukaemia (NEL): Meets all other criteria for CHR except may have thrombocytopenia (platelets greater than or equal to 20,000/mm^3 and less than 100,000/mm^3) and/or neutropenia (ANC greater than or equal to 0.5×10^9/L and less than 1.0×10^9/L). Return to chronic phase (RCP) = disappearance of features defining accelerated or blast phases but still in chronic phase.
Abbreviations: AP=accelerated phase; BP=blast phase; Ph+=Philadelphia chromosome-positive; CP=chronic phase; CML=chronic myelogenous leukaemia; K-M=Kaplan-Meier; N/n=number of patients; N/A=not applicable; N/R=not reached as of minimum follow-up; N/E=not estimable; CI=confidence interval; MCyR=major cytogenetic response; CCyR=complete cytogenetic response; OHR=overall haematological response; CHR=complete haematological response.

[a] Includes patients (N) with a valid baseline assessment. The analyses allow baseline responders who maintained response post-baseline to be responders. Minimum follow-up time (time from last patient first dose to data snapshot date) of 60 months for CP treated with imatinib only and, 48 months for CP treated with imatinib and at least one1 other TKI, AP and BP.

[b] Includes patients (N) who attained or maintained MCyR.

[c] Years 2 (Month 24) and 5 (60 months) for CP treated with imatinib only and Years 1 (Month 12) and 4 (48 months) for CP treated with imatinib and at least 1 other TKI, AP, and BP.

[d] Sample size (N) includes patients with a valid baseline haematological assessment. These analyses allow baseline responders who maintained response post-baseline to be responders.

[e] Includes patients (N) who attained or maintained CHR for CP patients and OHR for AP and BP patients.

[f] Including patients (N) who received at least 1 dose of bosutinib.

Based on the limited clinical information from the Phase 1/2 study, some evidence of clinical activity was observed in patients with BCR-ABL mutations (see Table 6).

Table 6 - Response by baseline BCR-ABL mutation status in CP CML evaluable population: prior imatinib and dasatinib and/or nilotinib (third-line)

BCR-ABL mutation status at baseline	Incidence at baseline n (%)[a]	MCyR attained or maintained Resp/Eval[b] (%) N=112
Mutation assessed	96 (100.0)	34/92 (37.0)
No mutation	57 (59.4)	21/55 (38.2)
At least 1 mutation	39 (40.6)	13/37 (35.1)
Dasatinib resistant mutations	10 (10.4)	1/9 (11.1)
E255K/V	2 (2.0)	0/2
F317L	8 (8.3)	1/7 (14.3)
Nilotinib resistant mutations[c]	13 (13.5)	8/13 (61.5)
Y253H	6 (6.3)	5/6 (83.3)
E255K/V	2 (2.0)	0/2
F359C/I/V	7 (7.3)	5/7 (71.4)

Snapshot date: 02Oct2015
Note: Baseline mutations were identified before the patient's first dose of study drug.
Abbreviations: BCR-ABL=breakpoint cluster region-Abelson; CP=chronic phase; CML=chronic myelogenous leukaemia; MCyR=major cytogenetic response; N/n=number of patients; Resp=responders; Eval=evaluable.
[a] The percentage is based on number of patients with baseline mutation assessment.
[b] The evaluable population includes patients who had a valid baseline disease assessment.
[c] 2 patients had more than 1 mutation in this category.

One patient with the E255V mutation previously treated with nilotinib achieved CHR as best response.

In vitro testing indicated that bosutinib had limited activity against the T315I or the V299L mutation. Therefore, clinical activity in patients with these mutations is not expected.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with Bosulif in one or more subsets of the paediatric population in CML (see section 4.2 for information on paediatric use).

Conditional approval
This medicinal product has been authorised under a so-called "conditional approval" scheme. This means that further evidence on this medicinal product is awaited.

The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Absorption
Following administration of a single dose of bosutinib (500 mg) with food in healthy subjects, the absolute bioavailability was 34%. Absorption was relatively slow, with a median time-to-peak concentration (t_{max}) reached after 6 hours. Bosutinib exhibits dose proportional increases in AUC and C_{max}, over the dose range of 200 to 600 mg. Food increased bosutinib C_{max} 1.8-fold and bosutinib AUC 1.7-fold compared to the fasting state. In CML patients at steady state, C_{max} (geometric mean, coefficient of variation [CV]%) was 145 (14) ng/mL, and AUC_{ss} (geometric mean, CV%) was

2,700 (16) ng•h/mL after daily administration of bosutinib at 400 mg with food. After 500 mg bosutinib daily with food, C_{max} was 200 (6) ng/mL and AUC_{ss} was 3,640 (12) ng•h/mL. The solubility of bosutinib is pH-dependent and absorption is reduced when gastric pH is increased (see section 4.5).

Distribution

Following administration of a single intravenous dose of 120 mg bosutinib to healthy subjects, bosutinib had a mean (% coefficient of variation [CV]) volume of distribution of 2,331 (32) L, suggesting that bosutinib is extensively distributed to extra-vascular tissue.

Bosutinib was highly bound to human plasma proteins *in vitro* (94%) and *ex vivo* in healthy subjects (96%), and binding was not concentration-dependent.

Biotransformation

In vitro and *in vivo* studies indicated that bosutinib (parent compound) undergoes predominantly hepatic metabolism in humans. Following administration of single or multiple doses of bosutinib (400 or 500 mg) to humans, the major circulating metabolites appeared to be oxydechlorinated (M2) and *N*-desmethylated (M5) bosutinib, with bosutinib *N*-oxide (M6) as a minor circulating metabolite. The systemic exposure of *N*-desmethylated metabolite was 25% of the parent compound, while the oxydechlorinated metabolite was 19% of the parent compound. All 3 metabolites exhibited activity that was ≤ 5% that of bosutinib in a Src-transformed fibroblast anchorage-independent proliferation assay. In faeces, bosutinib and *N*-desmethyl bosutinib were the major drug-related components. *In vitro* studies with human liver microsomes indicated that the major cytochrome P450 isozyme involved in the metabolism of bosutinib is CYP3A4 and drug interaction studies have shown that ketoconazole and rifampicin had marked effect on the pharmacokinetics of bosutinib (see section 4.5). No metabolism of bosutinib was observed with CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A5.

Elimination

In healthy subjects given a single intravenous dose of 120 mg bosutinib, the mean (%CV) terminal elimination half-life was 35.5 (24) hours, and the mean (%CV) clearance was 61.9 (26) L/h. In a mass-balance study with oral bosutinib, an average of 94.6% of the total dose was recovered in 9 days; faeces (91.3%) was the major route of excretion, with 3.29% of the dose recovered in urine. Seventy-five percent of the dose was recovered within 96 hours. Excretion of unchanged bosutinib in urine was low with approximately 1% of the dose in both healthy subjects and those with advanced malignant solid tumours.

Special populations

Hepatic impairment

A 200 mg dose of bosutinib administered with food was evaluated in a cohort of 18 hepatically impaired subjects (Child-Pugh classes A, B, and C) and 9 matched healthy subjects. C_{max} of bosutinib in plasma increased 2.4-fold, 2-fold, and 1.5-fold, respectively, in Child-Pugh classes A, B, and C; and bosutinib AUC in plasma increased 2.3-fold, 2-fold, and 1.9-fold, respectively. The $t_{½}$ of bosutinib increased in hepatic impaired patients as compared to the healthy subjects.

Renal impairment

In a renal impairment study, a single dose of 200 mg bosutinib was administered with food to 26 subjects with mild, moderate, or severe renal impairment and to 8 matching healthy volunteers. Renal impairment was based on CL_{Cr} (calculated by the Cockcroft-Gault formula) of < 30 mL/min (severe renal impairment), 30 ≤ CL_{Cr} ≤ 50 mL/min (moderate renal impairment), or 50 < CL_{Cr} ≤ 80 mL/min (mild renal impairment). Subjects with moderate and severe renal impairment had an increase in AUC over healthy volunteers of 35% and 60%, respectively. Maximal exposure C_{max} increased by 28% and 34% in the moderate and severe groups, respectively. Bosutinib exposure was not increased in subjects with mild renal impairment. The elimination half-life of bosutinib in subjects with renal impairment was similar to that in healthy subjects.

Dose adjustments for renal impairment were based on the results of this study, and the known linear pharmacokinetics of bosutinib in the dose range of 200 to 600 mg.

Age, gender and race
No formal studies have been performed to assess the effects of these demographic factors. Population pharmacokinetic analyses in patients with Ph+ leukaemia or malignant solid tumour indicate that there are no clinically relevant effects of age, gender, body weight, race.

Paediatric population
Bosulif has not yet been studied in children less than 18 years of age.

5.3 Preclinical safety data

Bosutinib has been evaluated in safety pharmacology, repeated dose toxicity, genotoxicity, reproductive toxicity, and photoxicity studies.

Safety pharmacology
Bosutinib did not have effects on respiratory functions. In a study of the central nervous system (CNS), bosutinib treated rats displayed decreased pupil size and impaired gait. A no observed effect level (NOEL) for pupil size was not established, but the NOEL for impaired gait occurred at exposures approximately 11-times the human exposure resulting from the clinical dose of 400 mg and 8-times the human exposure resulting from the clinical dose of 500 mg (based on unbound C_{max} in the respective species). Bosutinib activity *in vitro* in hERG assays suggested a potential for prolongation of cardiac ventricular repolarisation (QTc). In an oral study of bosutinib in dogs, bosutinib did not produce changes in blood pressure, abnormal atrial or ventricular arrhythmias, or prolongation of the PR, QRS, or QTc of the ECG at exposures up to 3-times the human exposure resulting from the clinical dose of 400 mg and 2-times the human exposure resulting from the clinical dose of 500 mg (based on unbound C_{max} in the respective species). A delayed increase in heart rate was observed. In an intravenous study in dogs, transient increases in heart rate and decreases in blood pressure and minimal prolongation of the QTc (< 10 msec) were observed at exposures ranging from approximately 6-times to 20-times the human exposure resulting from the clinical dose of 400 mg and 4-times to 15-times the human exposure resulting from the clinical dose of 500 mg (based on unbound C_{max} in the respective species). The relationship between the observed effects and medicinal product treatment were inconclusive.

Repeated-dose toxicity
Repeated-dose toxicity studies in rats of up to 6 months in duration and in dogs up to 9 months in duration revealed the gastrointestinal system to be the primary target organ of toxicity of bosutinib. Clinical signs of toxicity included foecal changes and were associated with decreased food consumption and body weight loss which occasionally led to death or elective euthanasia.

Histopathologically, luminal dilation, goblet cell hyperplasia, haemorrhage, erosion, and oedema of the intestinal tract, and sinus erythrocytosis and haemorrhage in the mesenteric lymph nodes, were observed. The liver was also identified as a target organ in rats. Toxicities were characterised by an increase in liver weights in correlation with hepatocellular hypertrophy which occurred in the absence of elevated liver enzymes or microscopic signs of hepatocellular cytotoxicity, and is of unknown relevance to humans. The exposure camparison across species indicates that exposures that did not elicit adverse events in the 6- and 9-month toxicity studies in rats and dogs, respectively, were similar to the human exposure resulting from a clinical dose of 400 mg or 500 mg (based on unbound AUC in the respective species).

Genotoxicity
Genotoxicity studies in bacterial *in vitro* systems and in mammalian *in vitro* and *in vivo* systems with and without metabolic activation did not reveal any evidence for a mutagenic potential of bosutinib.

Reproductive toxicity and development toxicity
In a rat fertility study, fertility was slightly decreased in males. Females were observed with increased embryonic resorptions, and decreases in implantations and viable embryos. The dose at which no adverse reproductive effects were observed in males (30 mg/kg/day) and females (3 mg/kg/day) resulted in exposures equal to 0.6-times and 0.3-times, respectively, the human exposure resulting from the clinical dose of 400 mg, and 0.5-times and 0.2-times, respectively, the human exposure resulting from the clinical dose of 500 mg (based on unbound AUC in the respective species). An effect on male fertility cannot be excluded (see Section 4.6).

Foetal exposure to bosutinib-derived radioactivity during pregnancy was demonstrated in a placental transfer study in gravid Sprague-Dawley rats. In a separate study, bosutinib was administered orally to pregnant rats during the period of organogenesis at doses of 1, 3, and 10 mg/kg/day. This study did not expose pregnant rats to enough bosutinib to fully evaluate adverse outcomes. In a rabbit developmental toxicity study at the maternally toxic dose, there were foetal anomalies observed (fused sternebrae, and 2 foetuses had various visceral observations), and a slight decrease in foetal body weight. The exposure at the highest dose tested in rabbits (10 mg/kg) that did not result in adverse foetal effects was 0.9-times and 0.7-times the human exposure resulting from the clinical dose of 400 or 500 mg, respectively (based on unbound AUC in the respective species).

Following a single oral (10 mg/kg) administration of [^{14}C] radiolabelled bosutinib to lactating Sprague-Dawley rats, radioactivity was readily excreted into breast milk as early as 0.5 hr after dosing. Concentration of radioactivity in milk was up to 8-fold higher than in plasma. This allowed measurable concentrations of radioactivity to appear in the plasma of nursing pups.

Carcinogenicity
Bosutinib was not carcinogenic in the 2-year rat carcinogenicity study.

Phototoxicity
Bosutinib has demonstrated the ability to absorb light in the UV-B and UV-A range and is distributed into the skin and uveal tract of pigmented rats. However, bosutinib did not demonstrate a potential for phototoxicity of the skin or eyes in pigmented rats exposed to bosutinib in the presence of UV radiation at bosutinib exposures up to 3-times and 2-times the human exposure resulting from the clinical dose of 400 or 500 mg, respectively (based on unbound C_{max} in the respective species).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose (E460)
Croscarmellose sodium (E468)
Poloxamer 188
Povidone (E1201)
Magnesium stearate (E470b)

Film coating
Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol 3350
Talc (E553b)

Additionally for Bosulif 100 mg film-coated tablets
Iron oxide yellow (E172)

Additionally for Bosulif 500 mg film-coated tablets
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Bosulif 100 mg film-coated tablets
White opaque 3-ply PVC/ACLAR/PVC blister sealed with push-through foil backing containing either 14 or 15 tablets.

Each carton contains 28 or 30 tablets (2 blisters per pack) or 112 tablets (8 blisters per pack).

Bosulif 500 mg film-coated tablets
White opaque 3-ply PVC/ACLAR/PVC blister sealed with push-through foil backing containing either 14 or 15 tablets.

Each carton contains 28 or 30 tablets (2 blisters per pack).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Ltd
Ramsgate Road
Sandwich, Kent CT13 9NJ
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

Bosulif 100 mg film-coated tablets
EU/1/13/818/001
EU/1/13/818/002
EU/1/13/818/005

Bosulif 500 mg film-coated tablets
EU/1/13/818/003
EU/1/13/818/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 March 2013
Date of latest renewal: 8 February 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Pfizer Manufacturing Deutschland GmbH
Mooswaldallee 1
D-79090 Freiburg
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
To conduct a single-arm open-label, multi-centre efficacy and safety study of bosutinib in patients with Philadelphia chromosome-positive chronic myelogenous leukaemia (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.	Final Clinical Study Report: 30 September 2018

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Bosulif 100 mg film-coated tablets
Bosutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100 mg bosutinib (as monohydrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets.
30 film-coated tablets.
112 film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich, Kent, CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/818/001	(28 film-coated tablets)
EU/1/13/818/002	(30 film-coated tablets)
EU/1/13/818/005	(112 film-coated tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Bosulif 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Bosulif 100 mg film-coated tablets
Bosutinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Bosulif 500 mg film-coated tablets
Bosutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 500 mg bosutinib (as monohydrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 Film-coated tablets.
30 Film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich, Kent, CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/818/003	28 film-coated tablets
EU/1/13/818/004	30 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Bosulif 500 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Bosulif 500 mg film-coated tablets
Bosutinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Bosulif 100 mg film-coated tablets
Bosulif 500 mg film-coated tablets
bosutinib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Bosulif is and what it is used for

Bosulif contains the active substance bosutinib. It is used to treat adult patients who have a type of leukaemia called Philadelphia chromosome-positive (Ph-positive) Chronic Myeloid Leukaemia (CML) and are newly-diagnosed or for whom previous medicines to treat CML have either not worked or are not suitable. Ph-positive CML is a cancer of the blood which makes the body produce too many of a specific type of white blood cell called granulocytes.

If you have any questions about how Bosulif works or why this medicine has been prescribed for you, ask your doctor.

2. What do you need to know before you take take Bosulif

Do not take Bosulif
- if you are allergic to bosutinib or any of the other ingredients of this medicine (listed in section 6).
- if your doctor has told you that your liver has been damaged and is not working normally.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Bosulif:
- **if you have, or have had in the past, liver problems.** Tell your doctor if you have a history of liver problems including hepatitis (liver infection or inflammation) of any kind, or a history of any of the following signs and symptoms of liver problems: itching, yellow eyes or skin, dark urine, and pain or discomfort in the right upper stomach area. Your doctor should do blood tests

to check your liver function prior to your starting treatment with Bosulif and for the first 3 months of treatment with Bosulif, and as clinically indicated.

- **if you have diarrhoea and vomiting.** Tell your doctor if you develop any of the following signs and symptoms: an increase in the number of stools (bowel movements) per day over normal, an increase in episodes of vomiting, blood in your vomit, stools (bowel movements) or urine, or have black stools (tarry black bowel movements). You should ask your doctor if use of your treatment for vomiting may result in a greater risk of heart arrhythmias. In particular, you should ask your doctor if you want to use a medicine containing domperidone for the treatment of nausea and/or vomiting. Treatment of nausea or vomiting with such medicines together with Bosulif may result in a greater risk of dangerous heart arrhythmias.

- **if you suffer from bleeding problems.** Tell your doctor if you develop any of the following signs and symptoms such as abnormal bleeding or bruising without having an injury.

- **if you have an infection.** Tell your doctor if you develop any of the following signs and symptoms such as fever, problems with urine such as burning on urination, a new cough, or a new sore throat.

- **if you have fluid retention.** Tell your doctor if you develop any of the following signs and symptoms of fluid retention during Bosulif treatment such as swelling of the ankles, feet or legs; difficulty breathing chest pain or a cough (these may be signs of fluid retention in the lungs or chest).

- **if you have heart problems.** Tell your doctor if you have a heart disorders, such as arrhythmias or an abnormal electrical signal called “prolongation of the QT interval”. This is always important, but especially if you are experiencing frequent or prolonged diarrhoea as described above. If you faint (loss of consciousness) or have an irregular heartbeat while taking Bosulif, tell your doctor immediately, as this may be a sign of a serious heart condition.

- **if you have been told that you have problems with your kidneys.** Tell your doctor if you are urinating more frequently and producing larger amounts of urine with a pale colour or if you are urinating less frequently and producing smaller amounts of urine with a dark colour. Also tell your doctor if you are losing weight or have experienced swelling of your feet, ankles, legs, hands or face.

- **if you have ever had or might now have a hepatitis B infection.** This is because Bosulif could cause hepatitis B to become active again, which can be fatal in some cases. Patients will be carefully checked by their doctor for signs of this infection before treatment is started.

- **if you have or have had pancreas problems.** Tell your doctor if you develop abdominal pain or discomfort.

- **if you have any of these symptoms: serious skin rashes.** Tell your doctor if you develop any of the following signs and symptoms of painful red or purplish rash that spreads and blisters and/or other lesions begin to appear in the mucous membrane (e.g., mouth and lips).

- **if you notice any of these symptoms: pain in your side, blood in your urine or reduced amount of urine.** When your disease is very severe, your body may not be able to clear all the waste products from the dying cancer cells. This is called tumour lysis syndrome and can cause kidney failure and heart problems within 48 hours of the first dose of Bosulif. Your doctor will be aware of this and may ensure you are adequately hydrated and give you other medicines to help prevent it.

Children and adolescents
Bosulif is not recommended for people whose age is under 18 years. This medicine has not been studied in children and adoloscents.

Other medicines and Bosulif
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription, vitamins, and herbal medicines. Some medicines can affect the levels of Bosulif in your body. You should inform your doctor if you are taking medicines containing active substances such as those listed below:

The following active substances may increase the risk of side effects with Bosulif:
- ketoconazole, itraconazole, voriconazole, posaconazole and fluconazole, used to treat fungal infections.
- clarithromycin, telithromycin, erythromycin, and ciprofloxacin, used to treat bacterial infections.
- nefazodone, used to treat depression.
- mibefradil, diltiazem and verapamil, used to lower blood pressure in people with high blood pressure.
- ritonavir, lopinavir/ritonavir, indinavir, nelfinavir, saquinavir, atazanavir, amprenavir, fosamprenavir and darunavir, used to treat human immunodeficiency virus (HIV)/AIDS.
- boceprevir and telaprevir, used to treat hepatitis C.
- aprepitant, used to prevent and control nausea (feeling sick) and vomiting.
- imatinib, used to treat a type of leukaemia.
- crizotinib, used to treat a type of lung cancer called non-small cell lung cancer.

The following active substances may reduce the effectiveness of Bosulif:
- rifampicin, used to treat tuberculosis.
- phenytoin and carbamazepine, used to treat epilepsy.
- bosentan, used to lower high blood pressure in the lungs (pulmonary artery hypertension).
- nafcillin, an antibiotic used to treat bacterial infections.
- St. John's Wort (a herbal preparation obtained without a prescription), used to treat depression.
- efavirenz and etravirine, used to treat HIV infections/AIDS.
- modafinil, used to treat certain types of sleep disorders.

These medicines should be avoided during your treatment with Bosulif. If you are taking any of them, tell your doctor. Your doctor may change the dose of these medicines, change the dose of Bosulif, or switch you to a different medicine.

The following active substances may affect the heart rhythm:
- amiodarone, disopyramide, procainamide, quinidine and sotalol used to treat heart disorder.
- chloroquine, halofantrine used to treat malaria.
- clarithromycin and moxifloxacin antibiotics used to treat bacterial infections.
- haloperidol, used to treat psychotic disease such as schizophrenia.
- domperidone, used to treat nausea and vomiting or to stimulate breast milk production.
- methadone, used to treat pain.

These medicines should be taken with caution during your treatment with Bosulif. If you are taking any of them, tell your doctor.

The medicines listed here may not be the only ones that could interact with Bosulif.

Bosulif with food and drink
Do not take Bosulif with grapefruit or grapefruit juice, as it may increase the risk of side effects.

Pregnancy and breast-feeding
Discuss contraception with your doctor if there is any possibility that you may become pregnant. Vomiting or diarrhoea may reduce the effectiveness of oral contraceptives.

Bosulif could harm an unborn baby, so it should not be used unless considered necessary during pregnancy. Ask your doctor for advice before taking Bosulif if you are pregnant or might become pregnant.

There is a risk that treatment with Bosulif will lead to decreased fertility and you may wish to seek advice about sperm storage before the treatment starts.

If you are breast-feeding, tell your doctor. Do not breast-feed during treatment with Bosulif as it could harm your baby.

Driving and using machines
If you experience dizziness, have blurred vision or feel unusually tired, do not drive or operate machines until these side effects have gone away.

3. How to take Bosulif

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Bosulif will only be prescribed to you by a doctor with experience in medicines to treat leukaemia.

Dosage and method of administration
The recommended dose is 400 mg once daily for patients with newly-diagnosed CML. The recommended dose is 500 mg once daily for patients whose previous medicines to treat CML have either not worked or are not suitable. In the event that you have moderate or severe kidney problems, your doctor will reduce your dose by 100 mg once daily for moderate kidney problems and by an additional 100 mg once daily for severe kidney problems. Your doctor may adjust the dose using the 100 mg tablets depending upon your medical conditions, upon your response to treatment and/or on any side effect you may experience. Take the tablet(s) in the morning with food. Swallow the tablet(s) whole with water.

If you take more Bosulif than you should
If you accidentally take too many Bosulif tablets or a higher dose than you need, contact a doctor for advice right away. If possible, show the doctor the pack, or this leaflet. You may require medical attention.

If you forget to take Bosulif
If dose is missed by less than 12 hours, take your recommended dose. If a dose is missed by more than 12 hours, take your next dose at your regular time on the following day.
Do not take a double dose to make up for the forgotten tablets.

If you stop taking Bosulif
Do not stop taking Bosulif unless your doctor tells you to do so. If you are not able to take the medicine as your doctor prescribed or you feel you do not need it anymore, contact your doctor right away.

If you have any further questions on the use of this medicine ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

You must immediately contact your doctor if you experience any of those serious side effects (see also section 2 “What you need to know before you take Bosulif”):

Blood disorders. Tell your doctor right away if you have any of these symptoms: bleeding, fever or easy bruising (you might have blood or lymphatic system disorder).

Liver disorders. Tell your doctor right away if you have any of these symptoms: itching, yellow eyes or skin, dark urine, and pain or discomfort in the right upper stomach area or fever.

Stomach/intestinal disorders. Tell your doctor if you develop stomach pain, heartburn, diarrhoea, constipation, nausea and vomiting.

Heart problems. Tell your doctor if you have a heart disorder, such as an abnormal electrical signal called “prolongation of the QT interval”, or if you faint (loss of consciousness) or have an irregular heart beat while taking Bosulif.

Hepatitis B reactivation. Recurrence (reactivation) of hepatitis B infection when you have had hepatitis B in the past (a liver infection).

Severe skin reactions. Tell your doctor right away if you have any of these symptoms: painful red or purplish rash that spreads and blisters and/or other lesions begin to appear in the mucous membrane (e.g. mouth and lips).

Side effects with Bosulif may include:

Very common side effects (may affect more than 1 in 10 people):
- reduction in the number of platelets, red blood cells and/or neutrophils (type of white blood cells).
- diarrhoea, vomiting, stomach pain, nausea.
- fever, swelling of hands, feet or face, fatigue, weakness.
- respiratory tract infection.
- nasopharyngitis.
- changes in blood test to determine if Bosulif is affecting your liver and/or pancreas.
- decrease of appetite.
- joint pain, back pain.
- headache.
- skin rash, which may be itchy and/or generalised.
- cough.
- shortness of breath.

Common side effects (may affect up to 1 in 10 people):
- low white blood cells count (leukopenia).
- stomach irritation (gastritis), bleeding from the stomach or intestine.
- chest pain, pain.
- toxic damage to the liver, abnormal hepatic function including liver disorder.
- infection of the lung (pneumonia), influenza, bronchitis.
- defect in cardiac rhythm that predisposes to fainting, dizziness and palpitation.
- increase in blood pressure.
- high level of potassium in the blood, low level of phosphorus in the blood, excessive loss of body fluid (dehydration).
- pain in the muscles.
- feeling of instability (dizziness), alteration of the sense of taste (dysgeusia).
- acute kidney failure, kidney failure, kidney impairment.
- fluid on the lungs (pleural effusion).

- fluid around the heart (pericardial effusion).
- ringing in the ears (tinnitus).
- itching, urticaria (hives), acne.

Uncommon side effects (may affect up to 1 in 100 people):
- fever associated with low white blood cell count (febrile neutropenia).
- acute inflammation of the pancreas (acute pancreatitis).
- damage to the liver.
- life-threatening allergic reaction (anaphylactic shock).
- abnormal build-up of fluid in the lungs (acute pulmonary oedema).
- respiratory failure.
- allergic reaction.
- abnormally high blood pressure in the arteries of the lungs (pulmonary hypertension).
- skin eruption.
- inflammation of the sac-like covering of the heart (pericarditis).
- a marked decrease in the number of granulocytes (a type of white blood cells).

Rare side effects (may affect up to 1 in 1,000 people):
- severe skin disorder (erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis) due to an allergic reaction, exfoliative (scaly, peeling) rash.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Bosulif

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the blister foil and carton after "EXP". The expiry date refers to the last day of that month.
- This medicine does not require any special storage conditions.
- Do not use this medicine if you notice that the pack is damaged or shows signs of tampering.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Content of the pack and other information

What Bosulif contains
- The active substance is bosutinib. Bosulif film-coated tablets come in different strengths.
  Bosulif 100 mg: each film-coated tablet contains 100 mg bosutinib (as monohydrate).
  Bosulif 500 mg: each film-coated tablet contains 500 mg bosutinib (as monohydrate).

- The other ingredients are: microcrystalline cellulose (E460), croscarmellose sodium (E468), poloxamer 188, povidone (E1201) and magnesium stearate (E470b). The tablet film-coating contains polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, talc (E553b) and iron oxide yellow (E172, for Bosulif 100 mg) or iron oxide red (E172, for Bosulif 500 mg).

What Bosulif looks like and contents of the pack
Bosulif 100 mg are yellow, oval biconvex, film-coated tablets debossed with "Pfizer" on one side and "100" on the other side.

Bosulif 100 mg is available in blisters containing either 14 or 15 film-coated tablets. Each carton contains 28 or 30 film-coated tablets (2 blisters) or 112 film-coated tablets (8 blisters).

Bosulif 500 mg are red, oval biconvex, film-coated tablets debossed with “Pfizer” on one side and “500” on the other side.
Bosulif 500 mg is available in blisters containing either 14 or 15 film-coated tablets. Each carton contains 28 or 30 film-coated tablets (2 blisters).

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Pfizer Limited
Ramsgate Road
Sandwich, Kent CT13 9NJ
United Kingdom

Manufacturer
Pfizer Manufacturing Deutschland GmbH
Betriebsstatte Freiburg
Mooswaldallee 1
Freiburg
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

Belgique / België /Belgien
Pfizer S.A. / N.V.
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This medicine has been given “conditional approval”.
This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.