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 chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukaemia (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
The recommended dose is 500 mg bosutinib once daily. In clinical trials, treatment with bosutinib continued until disease progression or until it was no longer tolerated by the patient.

Dose adjustments
In the Phase 2 clinical trial of adult patients with previously treated Ph+ leukaemia, dose escalation to 600 mg once daily with food was allowed in patients who did not experience severe or persistent

moderate-adverse reactions, under any of the following circumstances. A total of 85 patients (15.2%) who started treatment at </= 500 mg (n= 558) received dose escalations to 600 mg of bosutinib.

Circumstances for dose escalation
- Failure to achieve complete haematologic response (CHR) by Week 8
- Failure to achieve complete cytogenetic response (CCyR) by Week 12

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

Dose adjustments for adverse reactions
Dose adjustments for non-haematologic adverse reactions
If clinically significant moderate or severe non-haematological toxicity develops, bosutinib should be interrupted, and may be resumed at 400 mg once daily once the toxicity has resolved. If clinically appropriate, re-escalation of the dose to 500 mg once daily should be considered (see section 4.4).

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).

Dose adjustments for haematologic 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, reduce dose by 100 mg and resume treatment. If cytopoenia recurs, reduce dose by 100 mg upon recovery and resume treatment. Doses less than 300 mg/day have not been evaluated.

[a] ANC = absolute neutrophil count

Special populations
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 (AUC) in patients with moderate and severe renal impairment during studies was observed.

In patients with moderate renal impairment (creatinine clearance [CrCL] 30 to 50 mL/min, calculated by the Cockroft-Gault formula), the recommended dose of bosutinib is 400 mg daily (see sections 4.4 and 5.2).

In patients with severe renal impairment (CrCL < 30 mL/min, calculated by the Cockroft-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, under any of the following circumstances.

Circumstances for dose escalation
- Failure to achieve CHR by Week 8
- Failure to achieve CCyR by Week 12

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 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 (ALT, 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, and pulmonary 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. Patients with pretreated and advanced stage Ph+ leukemias in the global single-arm Phase 1/2 clinical trial showed a median decline from baseline in eGFR of 5.29 ml/min/1.73 m^2 at 3 months, of 7.11 ml/min/1.73 m^2 at 6 months and of 10.92 ml/min/1.73 m^2 at 36 months. Treatment-naïve CML patients showed a median decline from

baseline in eGFR of 5.06 ml/min/1.73 m^2 at 3 months, of 7.65 ml/min/1.73 m^2 at 6 months and of 15.62 ml/min/1.73 m^2 at 48 months. 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 preexisting 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 is 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).

CYP3A 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.

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).

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 870 Ph+ leukaemia patients received at least 1 dose of single-agent bosutinib. These patients were either newly diagnosed, Ph+ CP CML or were resistant or intolerant to prior therapy with Ph+ chronic, accelerated, or blast phase CML or Ph+ acute lymphoblastic leukaemia (ALL). Of these patients, 248 are from the Phase 3 study in previously untreated CML patients, 570 and 52 are from 2 Phase 1/2 studies in previously treated Ph+ leukaemias. The median duration of therapy was 16.6 months (range: 0.03 to 30.4 months), 11 months (range: 0.03 to 55.1 months), and 5.5 months (range: 0.3 to 30.4 months), respectively.

At least 1 adverse reaction of any toxicity grade was reported for 848 (97.5%) patients. The most frequent adverse reactions reported for ≥ 20% of patients were diarrhoea (78.5%), nausea (42.1%), thrombocytopenia (38.5%), vomiting (37.1%), abdominal pain (33.4%), rash (32.4%), anaemia (27.4%), pyrexia (23.4%), and alanine aminotransferase (ALT) increased (22.3%). At least 1 Grade 3 or Grade 4 adverse reaction was reported for 531 (61.0%) patients. The Grade 3 or Grade 4 adverse reactions reported for ≥ 5% of patients were thrombocytopenia (25.4%), anaemia (12.3%), neutropenia (11.5%), ALT increased (10.2%), diarrhoea (9.1%), rash (6.1%), lipase increased (5.2%) and aspartate aminotransferase (AST) increased (5.0%).

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 870 patients with newly diagnosed Ph+ CP CML or with Ph+ chronic, accelerated, or blast phase CML or Ph+ ALL resistant or intolerant to prior therapy and 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

System Organ Class	***Frequency***	***Adverse reactions***	***All Grades n (%)***	***Grade 3 n (%)***	***Grade 4 n (%)***
Infections and infestations	Very common	Respiratory tract infection[a]	99 (11.4)	4 (0.5)	0
	Common	Pneumonia[b]	45 (5.2)	21 (2.4)	5 (0.6)
		Influenza	47 (5.4)	2 (0.2)	0
		Bronchitis	27 (3.1)	1 (0.1)	0
		Nasopharyngitis	81 (9.3)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Uncommon	Tumour lysis syndrome*	4 (0.5)	2 (0.2)	0
Blood and lymphatic system disorders	Very common	Thrombocytopenia	335 (38.5)	127 (14.6)	94 (10.8)
		Neutropenia	141 (16.2)	67 (7.7)	33 (3.8)
		Anaemia	238 (27.4)	82 (9.4)	25 (2.9)
		Leukopenia	94 (10.8)	31 (3.6)	8 (0.9)
	Common	Febrile neutropenia	13 (1.5)	8 (0.9)	3 (0.3)
	Uncommon	Granulocytopenia	2 (0.2)	0	2 (0.2)

System Organ Class	*Frequency*	*Adverse reactions*	*All Grades n (%)*	*Grade 3 n (%)*	*Grade 4 n (%)*
Immune system disorders	Common	Hypersensitivity	12 (1.4)	7 (0.8)	0
	Uncommon	Anaphylactic shock	2 (0.2)	0	2 (0.2)
Metabolism and nutrition disorders	Very common	Decreased appetite	109 (12.5)	4 (0.5)	0
	Common	Dehydration	20 (2.3)	2 (0.2)	0
		Hyperkalaemia	23 (2.6)	2 (0.2)	1 (0.1)
		Hypophosphataemia	54 (6.2)	18 (2.1)	0
Nervous system disorders	Very common	Headache	148 (17.0)	9 (1.0)	3 (0.3)
	Common	Dizziness	74 (8.5)	2 (0.2)	0
		Dysgeusia	18 (2.1)	0	0
Ear and labyrinth disorders	Uncommon	Tinnitus	8 (0.9)	0	0
Cardiac disorders	Common	Pericardial effusion	16 (1.8)	2 (0.2)	1 (0.1)
		Electrocardiogram QT prolonged[c]	10 (1.1)	1 (0.1)	0
	Uncommon	Pericarditis	1 (0.1)	1 (0.1)	0
Vascular disorders	Common	Hypertension[d]	48 (5.5)	14 (1.6)	0
Respiratory, thoracic and mediastinal disorders	Very common	Cough	125 (14.4)	0	0
	Common	Dyspnoea	82 (9.4)	15 (1.7)	3 (0.3)
		Pleural effusion	52 (6.0)	14 (1.6)	1 (0.1)
	Uncommon	Respiratory failure	5 (0.6)	1 (0.1)	1 (0.1)
		Acute pulmonary oedema	3 (0.3)	1 (0.1)	1 (0.1)
		Pulmonary hypertension	4 (0.5)	1 (0.1)	0
Gastrointestinal disorders	Very common	Diarrhoea	683 (78.5)	78 (9.0)	1 (0.1)
		Vomiting	323 (37.1)	25 (2.9)	0
		Nausea	366 (42.1)	10 (1.1)	0
		Abdominal pain[e]	291 (33.4)	15 (1.7)	0
	Common	Gastritis	25 (2.9)	3 (0.3)	1 (0.1)
	Uncommon	Acute pancreatitis	3 (0.3)	2 (0.2)	1 (0.1)
		Gastrointestinal haemorrhage[f]	6 (0.7)	5 (0.6)	0
Hepatobiliary disorders	Very common	Alanine aminotransferase increased	194 (22.3)	79 (9.1)	10 (1.1)
		Aspartate aminotransferase increased	160 (18.4)	41 (4.7)	3 (0.3)
	Common	Hepatotoxicity[g]	15 (1.7)	5 (0.6)	1 (0.1)
		Hepatic function abnormal	27 (3.1)	8 (0.9)	3 (0.3)
		Blood bilirubin increased	33 (3.8)	8 (0.9)	0
		Gamma-glutamyltransferase increased	29 (3.3)	7 (0.8)	0
	Uncommon	Liver Injury	2 (0.2)	1 (0.1)	1 (0.1)

System Organ Class	*Frequency*	*Adverse reactions*	*All Grades n (%)*	*Grade 3 n (%)*	*Grade 4 n (%)*
Skin and subcutaneous tissue disorders	Very common	Rash[h]	282 (32.4)	51 (5.9)	2 (0.2)
	Common	Urticaria	26 (3.0)	2 (0.2)	1 (0.1)
		Acne	25 (2.9)	0	0
		Pruritus	71 (8.2)	3 (0.3)	0
	Uncommon	Erythema multiforme	1 (0.1)	0	1 (0.1)
		Exfoliative rash	6 (0.7)	1 (0.1)	0
		Drug eruption	5 (0.6)	1 (0.1)	0
	Not known	Stevens-Johnson Syndrome and Toxic epidermal necrolysis*	---	---	---
Musculoskeletal and connective tissue disorders	Very common	Arthralgia	96 (11.0)	3 (0.3)	0
	Common	Myalgia	49 (5.6)	3 (0.3)	0
		Back pain	72 (8.3)	7 (0.8)	1 (0.1)
Renal and urinary disorders	Common	Renal failure	13 (1.5)	2 (0.2)	1 (0.1)
	Uncommon	Renal failure acute	7 (0.8)	3 (0.3)	1 (0.1)
		Renal impairment	8 (0.9)	1 (0.1)	0
General disorders and administration site conditions	Very common	Pyrexia	204 (23.4)	6 (0.7)	1 (0.1)
		Oedema[i]	100 (11.5)	1 (0.1)	0
		Fatigue[j]	169 (19.4)	14 (1.6)	1 (0.1)
	Common	Chest pain[k]	61 (7.0)	4 (0.5)	1 (0.1)
		Pain	41 (4.7)	5 (0.6)	0
		Asthenia	86 (9.9)	7 (0.8)	2.(0.2)
Investigations	Common	Lipase increased	76 (8.7)	41 (4.7)	4 (0.5)
		Blood creatinine increased	42 (4.8)	2 (0.2)	0
		Blood amylase increased	31 (3.6)	7 (0.8)	0
		Blood creatine phosphokinase increased	28 (3.2)	3 (0.3)	2 (0.2)

The following terms have been combined:

[a] Respiratory tract infection, upper respiratory tract infection, lower respiratory tract infection, viral upper respiratory tract infection, respiratory tract infection viral.

[b] Pneumonia, bronchopneumonia, primary atypical pneumonia, lobar pneumonia.

[c] Electrocardiogram QTc prolonged, long QTc syndrome.

[d] Vascular hypertensive disorders, blood pressure increased

[e] Abdominal pain, upper abdominal pain, lower abdominal pain, abdominal discomfort, abdominal tenderness, gastrointestinal pain.

[f] Gastrointestinal haemorrhage, gastric haemorrhage, upper gastrointestinal haemorrhage.

[g] Hepatotoxicity, toxic hepatitis, cytolytic hepatitis.

[h] Rash, maculopapular rash, macular rash, pruritic rash, generalized rash, papular rash.

[i] Oedema, face oedema, localized oedema, peripheral oedema.

[j] Fatigue, malaise.

[k] Chest pain, chest discomfort.

***** ADR identified post-marketing

Description of selected adverse reactions

The descriptions included below are based on the safety population of 870 patients who received at least 1 dose of bosutinib in either a Phase 3 study in newly diagnosed Ph+ CP CML or in single-arm

Phase 1/2 clinical studies that enrolled patients who were resistant or intolerant to prior therapy with Ph+ chronic, accelerated, or blast phase CML, or Ph+ ALL.

Blood and lymphatic system disorders
Of the 224 (26%) patients with reports of adverse reactions of anaemia, 5 patients discontinued bosutinib due to anaemia. In these patients, the maximum toxicity of Grade 1 or 2 was experienced in 125 (56%) patients, Grade 3 in 76 patients (34%), and Grade 4 in 23 (10%) patients. Among these patients, the median time to first event was 28 days (range: 1 to 658 days) and the median duration per event was 12 days (range: 1 to 502 days).

Of the 135 (16%) patients with reports of adverse reactions of neutropenia, 13 patients discontinued bosutinib due to neutropenia. Maximum Grade 1 or 2 events were experienced by 37 (27%) patients. The maximum toxicity of Grade 3 neutropenia was experienced in 66 (49%) patients and of Grade 4 in 32 (24%) patients. The median time to first event was 56 days (range: 2 to 840 days) and the median duration per event was 14 days (range: 1 to 454 days).

Of the 326 (38%) patients with reports of adverse reactions of thrombocytopenia, 29 (9%) patients discontinued treatment with bosutinib due to thrombocytopenia. Maximum Grade 1 or 2 events were experienced by 115 (35%) patients. The maximum toxicity of thrombocytopenia of Grade 3 was experienced in 124 (38%) patients and Grade 4 in 87 (27%) patients. Among patients with thrombocytopenia adverse events, the median time to first event was 28 days (range: 1 to 968 days) and median duration per event was 14 days (range: 1 to 666 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 in the study was 28 days with a range of onset 6 to 841 days for ALT and 1 to 680 days for AST. The median duration of an event was 15 days (range, 1 to 336 days), and 14 days (range, 1 to 595 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 obvious causes in 1/1,209 (< 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 681 (78%) patients that experienced diarrhoea, 665 patients had drug-related events of diarrhoea and 8 patients discontinued bosutinib due to this event. Concomitant medicinal products were given to treat diarrhoea in 461 (68%) of patients. The maximum toxicity of diarrhoea was Grade 1 or 2 in 89% of patients, Grade 3 in 11% 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 594 days) and the median duration of any grade of diarrhoea was 2 days (range: 1 to 910 days).

Among the 681 patients with diarrhoea, 104 patients (15%) were managed with treatment interruption and of these 98 (94%) were rechallenged with bosutinib. Of those who were rechallenged, 95 (97%) did not have a subsequent event or did not discontinue bosutinib due to a subsequent event of diarrhoea.

Cardiac disorders
Three patients (0.3%) experienced QTcF interval prolongation (greater than 500 ms). Eight (0.9%) patients, including 2 of those with QTcF interval prolongation of greater than 500 ms, 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 pharmacologic 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 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 two 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 iin healthy subjects at the recommended 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 6 (1.1%) of 562 patients. In the Phase 3 clinical study in patients with newly diagnosed Ph+ CP CML, 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 imatinib-resistant or intolerant CML in chronic phase, accelerated phase, and blast phase.

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 haematologic response (OHR) and time to and duration of OHR. Other efficacy endpoints include transformation to AP/BP, progression free survival and overall survival for all cohorts.

Chronic phase

The efficacy results for Ph+ CP CML patients previously treated with imatinib and at least 1 additional TKI (minimum follow-up 25 months and median treatment duration of 8.6 months) and the results for Ph+ CP CML patients previously treated with only imatinib (minimum follow-up 24 months and median treatment duration of 22.1 months) are presented in Table 3. Efficacy results in the subgroup of patients corresponding to the approved indication are described below.

Efficacy for patients identified within the Phase 1/2 study population who failed either imatinib alone or imatinib in addition to 1 or both second-generation TKIs (dasatinib and nilotinib) and for whom, based on the presence of co-morbidities, a history of TKI intolerance, or a BCR-ABL resistance mutation, the remaining approved TKI(s) are not considered appropriate treatment options was reviewed. Of the 52 patients identified, 36 patients were in the CP CML subpopulation (21 who had previously received 2 prior TKIs and 15 who had received 1 prior TKI).

Of the 21 CP CML patients treated with bosutinib following failure of imatinib and 1 additional second-generation TKI identified, 9 of these patients had MCyR or better including 2 patients with complete molecular response (CMR), 1 patient with major molecular response (MMR), 4 patients with CCyR, and 2 patients with partial cytogenetic response (PCyR) and had a treatment duration exceeding 24 weeks. In addition, 7 other patients had a response of CHR on bosutinib treatment. Among the 9 patients with a response of MCyR or better, duration of MCyR ranged from 8 to 204 weeks with a treatment duration ranging from 35 to 215+ weeks.

There were 15 patients who received imatinib and no other second-generation TKI who met these criteria. Of these 15 patients with unmet medical need who had received prior imatinib only, 9 patients had a response on bosutinib treatment of MCyR or better, including 3 patients with CMR, 1 patient with MMR, 4 patients with CCyR, and 1 patients with PCyR with a duration of MCyR ranging from 12 to 155 weeks and a treatment duration ranging from 24 to 197+ weeks.

Accelerated and blast phase CML patients

The efficacy results for AP (minimum follow-up 12 months and median treatment duration of 10 months) and BP (minimum follow-up 18 months and median treatment duration of 2.8 months)

Ph+ CML patients are present in Table 3. Efficacy results in the subgroup of patients corresponding to the approved indication are described below.

There was also a subpopulation of 16 advanced phase patients (5 AP CML and 11 BP CML patients) that failed treatment with either imatinib alone or imatinib in addition to 1 or both second-generation TKIs (dasatinib and nilotinib) and for whom, based on the presence of co-morbidities, a history of TKI intolerance, or a BCR-ABL resistance mutation, the remaining approved TKI(s) were not considered appropriate treatment options. Of these, 4 of the 5 AP patients had notable treatment duration with a range from 46 to 114 weeks with responses including CMR (1 patient), CCyR (2 patients) and major haematologic response (MaHR) (1 patient) with 1 patient still on treatment. Among the 11 BP CML patients, 3 patients remained on treatment for more than 24 weeks with notable responses (2 patients with a CCyR and 1 patient with a MaHR) and a treatment duration ranging from 46 to 118 weeks with 1 patient still on treatment.

Table 3 - 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=266	N=110	N=69	N=54
MCyR, % (95% CI)	59.0 (52.9,65.0)	40.9 (31.6,50.7)	34.8 (23.7,47.2)	29.6 (18.0,43.6)
CCyR, % (95% CI)	48.1 (42.0,54.3)	31.8 (23.3,41.4)	24.6 (15.1,36.5)	20.4 (10.6,33.5)
Time to MCyR for responders only[b], wks (95% CI)	12.3 (12.1, 12.9)	12.3 (12.0, 22.3)	12 (8.1, 12.3)	8.2 (4.3, 12.1)
Duration of MCyR[b]	N=157	N=45	N=24	N=16
K-M at year 1 % (95% CI)	76.5 (68.5, 82.7)	74.0 (56.9, 85.1)	62.4 (38.6, 79.1)	7.9 (0.5, 29.8)
K-M at year 2 % (95% CI)	76.5 (68.5, 82.7)	70.9 (53.5,82.8)	N/A[c]	N/A[c]
Median , wks (95% CI)	N/R	N/R	73.0 (36.1, N/E)	28.9 (11.9, 29.6)
Cumulative hematologic response[d]	N=287	N=115	N=69	N=60
Overall, % (95% CI)	N/A	N/A	55.1 (42.6,67.1)	28.3 (17.5,41.4)
Major, % (95% CI)	N/A	N/A	46.4 (34.3,58.8)	18.3 (9.5,30.4)
Complete, % (95% CI)	85.0 (80.4, 88.9)	73.0 (64.0, 80.9)	34.8 (23.7,47.2)	15.0 (7.1,26.6)
Time to OHR for responders only, wks (95% CI)	N/A	N/A	12 (11.1, 12.1)	8.9 (4.1, 12.0)
Duration of CHR/OHR[e]	N=244	N=84	N=38	N=17
K-M at year 1 % (95% CI)	84.6 (79.0, 88.8)	72.6 (60.7, 81.5)	80.0 (60.5,90.5)	25.0 (7.8,47.2)
K-M at year 2, % (95% CI)	72.1 (65.2, 77.8)	67.4 (54.9, 77.2)	N/A[c]	N/A[c]
Median, wks (95% CI)	N/R	N/R	N/R	31.5 (28.9, 48.0)
Transformation to AP/BP[f]	N=288	N=118	N=63	N/A
On--treatment transformation, n	11	5	4	
Progression free survival[g]	N=288	N=119	N=76	N=64

	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
K-M at year 1, % (95% CI)	91.3 (86.8, 94.3)	78.3 (67.9, 85.6)	64.9 (51.8,75.3)	14.4 (6.0,26.4)
K-M at yea 2, % (95% CI)	80.6 (74.3,85.4)	75.1 (64.2,83.1)	N/A[c]	N/A[c]
Median, months (95% CI)	N/R	N/R	22.1 (14.6, N/E)	5.5 (3.2, 8.3)
Overall survival[g]	N=288	N=119	N=76	N=64
K-M at year 1, % (95% CI)	96.8 (94.0, 98.3)	91.4 (84.6, 95.3)	76.0 (64.7,84.2)	43.8 (31.3,55.6)
K-M at year 2, % (95% CI)	90.6 (86.5,93.5)	84.0 (75.8,89.6)	N/A[c]	N/A[c]
Median, months (95% CI)	N/R	N/R	N/R	11.1 (8.9, 19.8)

***** For efficacy results in the subgroup of patients corresponding to the approved indication, see text above.
Snapshot date: 15Feb12 for CP treated with imatinib and at least one other TKI and 28Mar11 for AP and BP and CP treated with imatinib only.
Abbreviations: K-M = Kaplan-Meier, N/A = Not applicable, N/R = Not reached, N/E = Not estimable, CI = Confidence Interval, MCyR = Major Cytogenetic Response, CCyR = Complete Cytogenetic Response, OHR = Overall Haematologic Response, CHR = Complete Haematologic Response.
Cytogenetic Response criteria: Major Cytogenetic response included Complete [0% Ph+ metaphases from bone marrow or < 1% positive cells from fluorescent in situ hybridization (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 haematologic response (OHR) = major haematologic response (complete haematologic response + no evidence of leukaemia) or return to chronic phase (RCP). All responses were confirmed after 4 weeks. Complete haematologic 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.

[a] Includes patients (N) with a valid baseline assessment. For CP patients, 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 24 months for CP treated with imatinib only, 25 months for CP treated with imatinib and at least one other TKI, 12 months for AP and 18 months for BP.

[b] For CP patients, includes patients (N) who attained or maintained MCyR.

[c] For AP and BP patients, 2-year data is not provided as minimum follow-up time is 12 and 18 months respectively.

[d] Sample size (N) includes patients with a valid baseline haematologic 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) with at least 1 post-baseline haematologic assessment.

[g] Including patients (N) who received at least one 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 4).

Table 4 - 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=110
Mutation assessed	86 (100.0)	32/82 (39.0)
No mutation	46 (53.5)	18/45 (40.0)
At least 1 mutation	40 (46.5)	14/37 (37.8)
Dasatinib resistant mutations	10 (11.6)	1/9 (11.1)
E255K/V	2 (2.3)	0/2
F317L	8 (9.3)	1/7 (14.3)
Nilotinib resistant mutations[c]	12 (14.0)	7/12 (58.3)
Y253H	6 (7.0)	5/6 (83.3)
E255K/V	2 (2.3)	0/2
F359C/V	5 (5.8)	3/5 (60.0)

Snapshot date: 15 February2012
Abbreviations: MCyR = Major Cytogenetic Response, Resp = responders, Eval = evaluable.
Note: Baseline mutations were identified before the patient's first dose of study drug.
[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] 1 subject 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.

Clinical study in chronic phase previously untreated CML
An international, multicentre, randomised, open-label, comparative Phase 3 efficacy and safety study was conducted in newly diagnosed Ph+ CP CML patients. Patients were randomised in a 1:1 fashion to treatment with either bosutinib 500 mg once daily or imatinib 400 mg once daily.

The primary objective of the study was to compare the CCyR at 1 year in patients with newly diagnosed Ph+ CP CML who received bosutinib compared with those who received imatinib. The primary objective was not met. Other efficacy objectives were to estimate the MMR, to estimate the duration of CCyR, CHR, and MMR, and to estimate the time to transformation to AP/BP.

A total of 250 patients randomised to receive bosutinib and 252 patients randomised to receive imatinib comprised the ITT population. Randomisation of patients was stratified by Sokal score and geographic region.

With a minimum of 24 months following the last patient’s first visit, and median treatment duration of 27.51 months, 62.9% of patients randomised to the bosutinib arm and 71.3% of patients randomised to the imatinib group were still receiving first-line treatment. Efficacy results are presented in Table 5. Based on these results, a positive benefit-risk of bosutinib in patients with previously untreated CML in the chronic phase has not been established.

Table 5 - Efficacy results in newly diagnosed patients with chronic phase CML, ITT population

	Bosutinib (n=250)	Imatinib (n=252)	p-value[a]
CCyR, % (95% CI)			
At 24 months[b]	57.6 (51.5, 63.7)	65.1 (59.2, 71.0)	0.081
At 12 months[c]	70.0 (64.3, 75.7)	67.9 (62.1, 73.6)	0.601
Cumulative CCyR[b]	78.8 (73.7, 83.9)	81.0 (76.1, 85.8)	0.546
MMR[d], % (95% CI)			
At 24 months[b]	46.8 (40.6, 53.0)	41.3 (35.2, 47.3)	0.205
At 12 months[b]	39.2 (33.1, 45.3)	25.4 (20.0, 30.8)	<0.001
Cumulative MMR[b]	61.2 (55.2, 67.2)	52.0 (45.8, 58.2)	0.035
Median time to MMR for responders only, weeks[b], (95% CI)	36.0 (35.4, 36.3)	48.3 (48.1, 59.7)	0.004
K-M estimate of OS at 24 months[b] % (95% CI)	97.4 (94.3, 98.8)	94.7 (91.0, 96.9)	n/a

[a] Analyses were stratified by Sokal-risk group (low, intermediate, high) and region. All p-values are 2-sided.
[b] Snapshot 26SEP11, Minimum follow-up time: 24 months
[c] Snapshot 31AUG10, Minimum follow-up time: 12 months
[d] MMR (3 log sensitivity) is defined as [(BCR copies/Abl copies)^{IS}] </= 0.001 and ABL copies >/= 3,000 and CMR (4.5 log sensitivity) is defined as [(BCR copies/Abl copies)^{IS}] </= 0.000032 and ABL copies >/= 25,614

No adjustment was made for multiple testing.
Abbreviations: n/a = not available, CI = Confidence Interval; CCyR = Complete Cytogenetic Response; MMR = Major Molecular Response, CMR = Complete Molecular Response, IS = International Scale.

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. The mean ± SD C_{max} value was 112 ± 29 ng/mL, and the mean AUC was 2740 ± 790 ng•h/mL. 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. After 15 daily dosing of bosutinib tablet with food in patients with CML, the mean C_{max} value was 200 ± 12 ng/mL, and the mean AUC was 3650 ± 425 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 a single dose of 500 mg bosutinib with food, bosutinib had a mean apparent volume of distribution of 9,560 ± 3,030 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 three 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
After a single oral dose of 500 mg bosutinib with food, the mean elimination half-life was approximately 34 hours, and the mean clearance (Cl/F) was 197 ± 57 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 (CrCl) (calculated by the Cockcroft-Gault formula) of < 30 mL/min (severe renal impairment), 30 ≤ CrCl ≤ 50 mL/min (moderate renal impairment), or 50 < CrCl ≤ 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.

Based on population pharmacokinetic modelling, a daily dose of 400 mg in patients with moderate renal impairment and a daily dose of 300 mg in patients with severe renal impairment are predicted to result in a similar AUC to that seen in patients with normal renal function receiving 500 mg daily.

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 > 8-fold those in CML patients receiving the 500 mg dose. Bosutinib activity *in vitro* in hERG assays suggested a potential for prolongation of cardiac ventricular repolarization (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 2-fold (comparing C_{max} and based on unbound fraction in the respective species) the clinical exposure at the 500 mg dose. 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 4.2 to 14.6-fold the clinical exposure following the 500 mg dose. The relationship between the observed effects and medicinal product treatment were inconclusive.

Repeated-dose toxicity
Repeated-dose toxicity studies in rats of up to six 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 characterized 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 or slightly exceeding the exposure in humans after multiple dosing of 500 mg.

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 0.5 and 0.2-times, respectively, the human exposure resulting from the clinical dose of 500 mg (based on unbound AUC in the respective species).

Foetal exposure to bosutinib-derived radioactivity during pregnancy was demonstrated in a placental transfer study in gravid Sprague-Dawley rats. The no observed adverse effect level (NOAEL) for developmental toxicity in rats occurred at exposures equal to 1.2-times the human exposure at the 500 mg dose. In a rabbit developmental toxicity study at the maternally toxic dose, there were foetal anomalies observed (fused sternebrae, and two 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 0.7-times that in humans at the 500 mg dose (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 at least 8-times greater than human exposure resulting from the 500 mg dose.

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: 24 March 2017

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

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Bosulif 100 mg

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

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Bosulif 500 mg

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 for whom previous medicines 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 three 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 color or if you are urinating less frequently and producing smaller amounts of urine with a dark color. 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 blood pressure in people with high blood pressure (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.

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 500 mg once daily. In the event that you have moderate or severe kidney problems, your doctor will reduce your dose to 400 mg once daily for moderate kidney problems and to 300 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
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).
- low white blood cells count (leukopenia).
- diarrhoea, vomiting, stomach pain, nausea.
- fever, swelling of hands, feet or face, fatigue, weakness.
- respiratory tract infection.
- changes in blood test to determine if Bosulif is affecting your liver.
- decrease of appetite.
- joint pain.
- headache.
- skin rash, which may be itchy and/or generalised.
- cough.

Common side effects (may affect up to 1 in 10 people):
- fever associated to low white blood cell count (febrile neutropenia).
- stomach irritation (gastritis).
- chest pain, pain.
- toxic damage to the liver, abnormal hepatic function including liver disorder.
- allergic reaction.
- infection of the lung (pneumonia), influenza, bronchitis, nasopharyngitis.
- changes in blood tests to determine if Bosulif is affecting your kidneys and/or pancreas.
- 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).
- back pain, pain in the muscles.
- feeling of instability (dizziness), alteration of the sense of taste (dysgeusia).
- kidney failure.
- fluid on the lungs (pleural effusion).
- shortness of breath.
- itching, urticaria (hives), acne.

Uncommon side effects (may affect up to 1 in 100 people):
- acute inflammation of the pancreas (acute pancreatitis).
- damage to the liver.
- life-threatening allergic reaction (anaphylactic shock).
- acute kidney failure, kidney impairment.
- abnormal build-up of fluid in the lungs (acute pulmonary oedema).
- respiratory failure.
- abnormally high blood pressure in the arteries of the lungs (pulmonary hypertension).
- severe skin disorder (erythema multiforme) due to an allergic reaction, exfoliative (scaly, peeling) rash, skin eruption.
- a marked decrease in the number of granulocytes (a type of white blood cells).
- ringing in the ears (tinnitus).
- bleeding from the stomach or intestine.
- inflammation of the sac-like covering of the heart (pericarditis).

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:

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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