PRODUCT MONOGRAPH

Pr BOSULIF®

bosutinib tablets

Tablets, 100 mg, 400 mg§ and 500 mg, Oral

Protein-tyrosine kinase inhibitor

§ Not commercially available in Canada

® Wyeth LLC,
Pfizer Canada ULC, licensee
17,300 Trans-Canada Highway
Kirkland, Quebec
H9J 2M5

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[Pr]BOSULIF®

bosutinib tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablets 100 mg, 400 mg[§] and 500 mg	Coating: iron oxide yellow (100 mg), iron oxide yellow and iron oxide red (400 mg), iron oxide red (500 mg). Tablet: *For a complete listing see Dosage Forms, Composition and Packaging section.*

[§] Not commercially available in Canada

INDICATIONS AND CLINICAL USE

BOSULIF (bosutinib) is indicated for the treatment of adult patients with newly-diagnosed chronic phase (CP) Philadelphia chromosome positive chronic myelogenous leukemia (Ph+ CML).

Market authorization in patients with newly-diagnosed chronic phase Ph+ CML is based on major molecular response (MMR) rates in a Phase 3 clinical trial with a minimum of 12 months of follow-up (see CLINICAL TRIALS).

BOSULIF (bosutinib) is indicated for the treatment of chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML) in adult patients with resistance or intolerance to prior TKI therapy.

Market authorization in patients with resistance or intolerance to prior TKI therapy, is based on cytogenetic and hematologic response rates observed in a single-arm, Phase 1/ 2 study. Overall survival benefit has not been demonstrated (see CLINICAL TRIALS).

BOSULIF should only be prescribed by a qualified healthcare professional who is experienced in the use of antineoplastic therapy and in the treatment of chronic myeloid leukemia.

Geriatrics *(≥ 65 years of age)*: No clinically relevant age-related pharmacokinetic differences have been observed in the elderly.

Pediatrics *(< 18 years of age)*: The safety and efficacy of BOSULIF in patients less than 18 years of age have not been evaluated. No data are available.

CONTRAINDICATIONS

Do not use BOSULIF (bosutinib) in patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. Cases of Grade 3 or 4 drug hypersensitivity were reported in patients treated with BOSULIF in single-agent cancer studies.

Two cases (less than 0.2%) of Grade 4 drug-related anaphylactic shock were reported in patients treated with BOSULIF (see ADVERSE REACTIONS). For a complete listing of ingredients, see the Dosage Forms, Composition and Packaging section of the product monograph.

Do not use BOSULIF in patients with a known history of long QT syndrome or with a persistent QT interval of >480 ms (see ADVERSE REACTIONS).

Do not use BOSULIF in cases of uncorrected hypokalemia or hypomagnesemia (see ADVERSE REACTIONS).

Do not use BOSULIF in hepatically impaired patients. Higher risk of QT prolongation has been seen in patients with declining hepatic function (see ACTION AND CLINICAL PHARMACOLOGY, WARNINGS AND PRECAUTIONS, Special Populations, and ACTION AND CLINICAL PHARMACOLOGY, Other Considerations).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Drug interactions with inhibitors or inducers of CYP3A4. The concomitant use of BOSULIF with strong or moderate CYP3A4 inhibitors or inducers should be avoided (see Warnings and Precautions, Drug Interactions, Serious Drug and Drug-Food Interactions and Dosage and Administration)
- Gastrointestinal toxicity, including diarrhea (see Warnings and Precautions and Adverse Reactions)
- Hepatic toxicity, including Hy's Law case (see Warnings and Precautions and Adverse Reactions)
- Cardiac failure, including fatal outcomes (see Warnings and Precautions and Adverse Reactions)
- Fluid retention (including pleural effusion, pulmonary edema and pericardial effusion (see Warnings and Precautions and Adverse Reactions)
- Hemorrhage (see Warnings and Precautions and Adverse Reactions)
- QT interval prolongation (see Warnings and Precautions and Adverse Reactions)

General

CYP3A inhibitors:

Bosutinib exposure can be increased when administered concomitantly with CYP3A inhibitors. Avoid the concomitant use of strong or moderate CYP3A inhibitors (see DRUG INTERACTIONS, Serious Drug and Drug-Food Interactions).

CYP3A inducers:

Bosutinib exposure is decreased when administered concomitantly with CYP3A inducers. Avoid the concomitant use of strong or moderate CYP3A inducers (see DRUG INTERACTIONS, Drug-Drug Interactions).

Carcinogenesis and Mutagenesis

Cases of second primary malignancies have been reported in humans in clinical trials with BOSULIF (see ADVERSE REACTIONS).

In the 2-year rat carcinogenicity study, overall, no relevant bosutinib-related increase in neoplastic lesion was shown. Nonclinical studies showed that bosutinib was not genotoxic or mutagenic (see TOXICOLOGY).

Cardiovascular

In clinical studies, patients with uncontrolled or significant cardiac disease (e.g. recent myocardial infarction, congestive heart failure or unstable angina) were excluded.

QT Prolongation

In the Phase 1/ 2 clinical study, 1 patient (0.2%) experienced QTcF (corrected QT by the Fridericia method) intervals of greater than 500 ms. Seven (1.2%) of the patients experienced QTcF increases from baseline exceeding 60 ms. Patients with uncontrolled or significant cardiovascular disease, including QT interval prolongation, at baseline were excluded by protocol criteria from the clinical trials (see ADVERSE REACTIONS).

In the phase 3 study in patients newly diagnosed with CP CML treated with bosutinib 400 mg, there was 1 patient (0.4%) in the bosutinib treatment group and 0 patients in the imatinib treatment group who experienced corrected QT by the Fridericia method (QTcF) interval of greater than 500 msec.

In a Phase 3 study of newly diagnosed Ph+ CP CML patients treated with bosutinib 500 mg, two patients (0.8%) experienced QTcF interval greater than 500 ms in the BOSULIF treatment arm. In this study population, BOSULIF was associated with statistically significant decreases from baseline in heart rate of approximately 4 bpm at months 2 and 3 (see ADVERSE REACTIONS).

BOSULIF should be administered with caution to patients who have a history of or predisposition for QTc prolongation, who have uncontrolled or significant cardiac disease

including recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia, or who are taking medicinal products that are known to prolong the QT interval (e.g. anti-arrhythmic medicinal products and other substances that may prolong QT (see DRUG INTERACTIONS, Drug-Drug Interactions). The presence of hypokalaemia and hypomagnesaemia may further increase this effect. Monitoring for an effect on the QTc interval is advisable and a baseline ECG is recommended prior to initiating therapy with BOSULIF and as clinically indicated. Hypokalaemia or hypomagnesaemia must be corrected prior to BOSULIF administration and should be monitored periodically during therapy (see CONTRAINDICATIONS).

Patients with hepatic impairment who are receiving treatment with BOSULIF are at higher risk of developing QT interval prolongation (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Special Populations).

Cardiac Toxicity

Cardiac-related TEAEs were reported in 13.5% of patients in the Phase 1/ 2 study, with Grade 3 or 4 cardiac-related events reported in 5.4% of patients. Pericardial effusion (3.7%), atrial fibrillation (2.5%) (Grade 3 or 4 in 0.9%), cardiac failure congestive (2.3%), and tachycardia (1.8%) were most commonly reported. The following Grade 3 or 4 events of acute myocardial infarction (0.5%), cardiac failure and coronary artery disease (1% of patients each), coronary artery stenosis (0.4%), left ventricular dysfunction (0.4%), and pulmonary edema (0.2%) were reported in the phase 1/2 study. In the Phase 3 study in patients newly diagnosed with CP CML treated with bosutinib 400 mg, 5.2 % of patients in the BOSULIF arm experienced cardiac events (0.7% of patients with Grade 3 or 4) versus 5.3% of patients in the imatinib arm (1.1% with Grade 3 or 4). Electrocardiogram QT prolonged (1.5%), Atrial fibrillation (1.1%) and Sinus bradycardia (1.5%) were most commonly reported. The following Grade 3 or 4 events of angina (0.4%), atrial fibrillation (0.4%), supraventricular tachycardia (0.4%), coronary artery disease (0.4%), coronary artety occlusion (0.4%), acute coronary syndrome (0.4%) and pericardial effusion (0.4%) were reported.

In a Phase 3 study in patients newly diagnosed with CP CML treated with bosutinib 500 mg, 3.6 % of patients in the BOSULIF arm experienced cardiac events (0.8% with Grade 3 or 4) versus 1.6 % of patients in the imatinib arm (none with Grade 3 or 4)

Caution should be exercised in patients with a history of or predisposition to relevant cardiac disorders including recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia.

Fluid Retention

Treatment with BOSULIF is associated with fluid retention (pericardial effusion, pleural effusion, pulmonary edema, and/or peripheral edema).

In the Phase 3 clinical trial of 268 patients with newly-diagnosed CML in the bosutinib treatment group, 1 patient (0.4%) experienced severe fluid retention of Grade 3 pericardial effusion.

In the single-arm Phase 1/2 clinical study in 570 patients with Ph+ leukemias treated with prior therapy, severe (Grade 3 and 4) fluid retention was reported in 26 patients (4.9%). Twenty-four patients had a Grade 3 or 4 effusion (22 patients had Grade 3 or 4 pleural effusions [3.8%] and 7 patients [1%] had a Grade 3 or 4 pericardial effusion). Edema TEAEs were reported in 114 (20.0%) subjects, most commonly, edema peripheral in 56 (9.8%) and weight increased in 24 (4.2%) subjects. Eight subjects reported SAEs: pulmonary edema (3 subjects), edema (2 subjects), angioedema, circumoral edema, and edema peripheral (one subject each). One subject died due to pulmonary edema.

In a Phase 3 study in patients newly diagnosed with CP CML treated with BOSULIF 500 mg, 3 patients (1.2%) experienced acute pulmonary edema or pulmonary edema (all grades) in the setting of either a pleural effusion or a pericardial effusion.

Patients should be weighed regularly and monitored for signs and symptoms of fluid retention, and managed using standard of care treatment, such as diuretics. In addition, these events can also be managed by withholding BOSULIF temporarily, dose reduction, and/or discontinuation of BOSULIF (see DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS).

Gastrointestinal

Diarrhea and Vomiting

Patients with recent or ongoing clinically significant gastrointestinal disorder should use BOSULIF with caution and only after a careful benefit-risk assessment, as patients with recent or ongoing clinically significant gastrointestinal disorder (e.g. severe vomiting and/or diarrhea) were excluded from CML clinical studies. Treatment with BOSULIF is associated with events of diarrhea and vomiting. In the single-arm Phase 1/2 clinical study, 88.4% of patients treated with BOSULIF experienced events of gastrointestinal toxicity. Diarrhea, nausea and vomiting were reported in 82%, 47% and 39% of subjects, respectively. Overall, 8% of patients experienced severe Grade 3 /4 diarrhea and 2.1% of patients had SAEs of diarrhea. The median time of onset for diarrhea (all grades) was 2 days and the median duration per event was 2 days.

In the Phase 3 clinical trial in patients with newly-diagnosed Ph+ CML treated with BOSULIF 400 mg, diarrhea, nausea and vomiting were reported in 70%, 35% and 18% of subjects, respectively. Overall, 8% of patients experienced severe Grade 3 /4 diarrhea and 1.1% of patients had SAEs of diarrhea. The median time to onset for diarrhea (all grades) was 3 days and the median duration per event was 3 days.

In newly diagnosed CML CP patients treated with BOSULIF 500 mg, a higher rate of drug-related vomiting was reported in the BOSULIF-treated group (31.5%) relative to the imatinib-treated group (13.5%). In these CML CP patients, a higher rate of drug-related diarrhea was also observed in the Bosulif-treated group (65.7%) relative to imatinib-treated group (17.9%). Bosutinib patients who reported a treatment-emergent diarrhea, 45.8% have experienced an individual episode of diarrhea for more than 28 consecutive days. Patients with these events should be managed using standard of care treatment, including antidiarrheal medication, and/or fluid replacement. Since some antiemetics and antidiarrheals are associated with a risk of increased QT interval prolongation with the potential to induce “torsade de pointes”, concomitant treatment with these agents should be carefully considered. In addition, these events

can also be managed by withholding BOSULIF temporarily, dose reduction, and/or discontinuation of BOSULIF (see DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS).

Hematologic

Myelosuppression

Treatment with BOSULIF is associated with myelosuppression, defined as anemia, neutropenia, and thrombocytopenia. Myelosuppression events reported in 58% of subjects treated with BOSULIF in the Phase 1 /2 study. The most common treatment-emergent adverse events were thrombocytopenia (41%), anemia (30%) and neutropenia (19%). Myelosuppression events reported in 45.5% of subjects treated with BOSULIF in the Phase 3 study in patients newly diagnosed with CP CML treated with bosutinib 400 mg. The most common treatment-emergent adverse events were thrombocytopenia (23.9%), anemia (17.9%), and platelet count decreased (12.3%). Patients with Ph+ leukemias who are receiving BOSULIF should have a complete blood count (including platelet count) performed weekly for the first month and then monthly thereafter, or as clinically indicated. Myelosuppression can be managed by withholding BOSULIF temporarily, dose reduction, and/or discontinuation of BOSULIF (see DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS).

Hemorrhage

In the Phase 1/2 population, treatment-emergent adverse events of any severity grade related to bleeding events were commonly reported in 22.5% of patients. Thirty two (5.6%) patients had SAEs. Hemorrhage events included duodenal ulcer hemorrhage, eye hemorrhage, gastrointestinal hemorrhage, hematochezia, menorrhagia, operative hemorrhage, pericardial hemorrhage, rectal hemorrhage, retroperitoneal hemorrhage, subarachnoid hemorrhage, vaginal hemorrhage, and cerebral hemorrhage. There were four deaths associated with haemorrhagic events (gastrointestinal hemorrhage, subarachnoid hemorrhage, intraventricular hemorrhage and cerebral hemorrhage in one subject each). In the phase 3 study, treatment-emergent adverse events of any severity grade related to bleeding events were commonly reported in 15.3% of patients. Four patients (1.5%) patients had SAEs (uterine hemorrhage, post procedural hemorrhage, hematuria, and implant site hematoma) none of which were fatal.

Patients with coagulation dysfunction/low platelet counts should be closely monitoring during treatment with BOSULIF.

Hepatic/Biliary and Pancreatic

Hepatotoxicity

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

In the 268 patients from the safety population in the Phase 3 clinical trial in patients with newly-diagnosed CML in the bosutinib treatment group, the incidence of ALT elevation was 31% and AST elevation was 23%. Most cases of transaminase elevations occurred early in treatment; of patients who experienced transaminase elevations of any grade, 79% experienced their first event

within the first 3 months. The median time to onset of increased ALT and AST was 32 and 43 days, respectively, and the median duration was 20 and 15 days, respectively.

In the 570 patients from the safety population from the single arm phase 1/2 study, adverse events associated with liver function were reported in 146 (25.6%) patients overall. The incidence of ALT elevation was 17% for all grades (of which 6% were maximum Grade 3/4) and AST elevation was 14 % for all grades (of which 3% were maximum Grade 3/4). Most cases of transaminase elevations occurred early in treatment; of patients who experienced transaminase elevations of any grade, more than 80% experienced their first event within the first 3 months. The median time to onset of increased ALT and AST was 29 and 30 days, respectively, and the median duration for each was 21 days. Eighteen (3.2%) patients discontinued BOSULIF due to liver function-related events.

In clinical studies with patient with cancer, one case consistent with Hy's Law and drug induced liver injury (defined as concurrent elevations in ALT or AST greater than or equal to 3 x ULN with total bilirubin greater than 2 x ULN and alkaline phosphatase less than 2 x ULN) occurred in a breast cancer trial of BOSULIF in combination with letrozole. The patient recovered fully following discontinuation of BOSULIF.

Patients receiving BOSULIF should have monthly hepatic enzyme tests for the first three months of treatment, or as clinically indicated. Patients with transaminase elevations can be managed by withholding BOSULIF temporarily, dose reduction, and/or discontinuation of BOSULIF (see DOSAGE AND ADMINISTRATION, Dosing Considerations, Hepatic Impairment and ADVERSE REACTIONS).

Elevated Serum lipase /Amylase and Pancreatitis

Grade 3 or 4 elevation in serum lipase (4.9%) and amylase (1.2%) and Grade 3 or 4 acute pancreatitis (0.8%) has been observed with BOSULIF. 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 DOSAGE AND ADMINISTRATION, Recommended Dose and Dose Adjustment). In the phase 3 study, Grade 3 or 4 elevation in serum lipase (9.7%) and amylase (1.5%) and Grade 3 or 4 acute pancreatitis (0.4%) has been observed with BOSULIF.

Infections

Infections including fungal respiratory tract infection and nasopharyngitis, fungal pneumonia, pseudomonal sepsis, bacteraemia, urinary tract infections, and gastrointestinal infections occurred more frequently in newly diagnosed BOSULIF-treated CML CP patients (40.7%) relative to imatinib-treated CML CP patients (31.1%). Also 0.7% of subjects in the Phase 1 /2 study had Grade 3 or 4 cellulitis. BOSULIF may predispose patients who are immunocompromised or older patients to bacterial, fungal, viral or protozoan infections. In the Phase 1 /2 study, 53% of patients had events of infection (13.5% Grade 3 /4). Eighty (14.0%) patients had SAEs, some of which were fatal. Seven patients died due to infection events, 4 patients died due to pneumonia and 1 patient each died due to fungal infection, bacteremia, sepsis.

In the phase 3 study in patients newly diagnosed with CP CML treated with bosutinib 400 mg, infection was reported less frequently in the bosutinib arm (44.4%) than in the imatinib arm (47.2%). 0.4% of subjects had Grade 3 or 4 cellulitis. Nine patients had Grade 3 or 4 infection (3.4%) and thirteen (4.9%) patients had SAEs, none of which were fatal.

Immune

In the Phase 1/2 clinical study, hypogammaglobulinaemia was reported. Patients with immunocompromising diseases or risk factors for immunosuppression, such as patients with HIV, AIDS, or patients receiving immunosuppressive therapies, should be closely monitored for signs of immunotoxicity. Leukocytoclastic vasculitis occurred in 1 patient (0.3%).

Hepatitis B virus reactivation

Reactivation of hepatitis B virus (HBV) has occurred in patients who are chronic carriers of this virus after receiving a Bcr-Abl tyrosine kinase inhibitor (TKI). Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or death.

Patients should be tested for hepatitis B infection before initiating treatment with BOSULIF. Patients currently on BOSULIF should have baseline testing for hepatitis B infection if clinically indicated, in order to identify chronic carriers of the virus. Experts in liver disease and in the treatment of hepatitis B should be consulted before treatment is initiated in patients with positive hepatitis B serology (including those with active disease) and for patients who test positive for HBV infection during treatment. Carriers of HBV who require treatment with BOSULIF should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy.

Hypersensitivity

Cases of Grade 3 or 4 hypersensitivity, anaphylactic shock leading to hospitalization, and urticaria have been reported with BOSULIF in the phase 1/2 clinical study only. In the phase 3 study in patients newly diagnosed with CP CML, hypersensitivity events were reported in 5 patients (1.9%) in the bosutinib arm, of which none were serious.

A potential source of hypersensitivity reactions may also be the excipients in the BOSULIF formulation (polyethylene glycol 3350, poloxamer 188, povidone, or other excipients (see CONTRAINDICATIONS).

Sexual Function/Reproduction

Fertility

Human studies on male patients receiving BOSULIF and its effect on male fertility and spermatogenesis have not been performed. Studies in rats showed that fertility was slightly decreased in male rats treated with bosutinib. Female rats had increased embryonic resorptions and decreases in implantations and viable embryos. The dose at which no adverse reproductive

effects were observed in males and females resulted in exposures equal to 0.5 times and 0.2 times, respectively, the human exposure based on the clinical dose of 500 mg (based on unbound AUC in the respective species). In a rat pre- and postnatal development study, there were reduced number of pups born, decreased postnatal survival (including increased incidence of total litter loss), and decreased growth of offspring after birth (see TOXICOLOGY, Developmental Toxicity). BOSULIF has the potential to impair reproductive function and fertility in humans. Physicians should advise and counsel their male and female patients as appropriate (see Special Populations, Male Fertility and DETAILED PHARMACOLOGY).

Females of childbearing potential

Females of childbearing potential (i.e. females who are menstruating, amenorrheic from previous treatments, and/or perimenopausal) must be advised to use highly effective contraception during treatment with BOSULIF and for at least 1 month after the final dose. If pregnancy does occur during treatment, BOSULIF should be stropped and the patients should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counselling.

Tumour Lysis Syndrome

In the Phase 1/2 study, there were 4 patients (0.7%) with tumour lysis syndrome, 2 of whom had Grade 3 or 4 severity. In the phase 3 study in patients newly diagnosed with CP CML treated with bosutinib 400 mg, there was 1 patient (0.4%) with Grade 3 tumour lysis syndrome. Renal function should be closely monitored and adequate hydration should be maintained if tumour lysis syndrome is considered a substantial risk.

Musculoskeletal

Changes in Bone Density

In the Phase 1/2 study, the frequency of fractures (including cervical, vertebral, clavicle, facial bones, foot, hand, humerus, rib, tooth, and upper limb) was reported to be 1.8%, with tooth fracture reported to be most common (0.4%). Grade 3 or 4 humerus fracture and rib fracture were reported in 0.2%, each (see ADVERSE DRUG REACTIONS). In the Phase 3 study in newly diagnosed CML CP patients treated with BOSULIF 500 mg, the frequency of fractures was 1.2% in the BOSULIF arm versus 0.4% in the imatinib arm. In addition, hypophosphataemia was reported in patients treated with BOSULIF.

In the Phase 3 study in newly diagnosed CML CP patients treated with BOSULIF 400 mg, the frequency of fractures (including hand, foot, ankle, radius, rib, spinal and tooth) was 2.8% in the BOSULIF arm with each event reported once. There were no reports of Grade 3 or 4 fractures.

In addition, hypophosphataemia (including blood phosphorus decreased) was reported in 6 patients (2.3%) treated with BOSULIF and 17 patients (6.4%) treated with imatinib.

Patients with endocrine abnormalities (e.g. hyperparathyroidism) and severe osteoporosis treated with BOSULIF could be at greater risk from the impact of bone mineralization abnormalities,

and should be monitored closely for changes in bone and mineral abnormalities, including bone density (see Monitoring and Laboratory Tests).

Renal and Urinary

A decline over time in estimated glomerular filtration rate (eGFR) was observed in CML patients receiving BOSULIF (see ADVERSE REACTIONS, Abnormal Hematologic and Clinical Chemistry Findings).

For patients with advanced phase leukemia, there appeared to be a more significant decline in eGFR at the same time point. While on treatment, over half (55%) of patients had at least trace or positive protein detected on spot check urinalyses, compared to 21% at baseline. Renal TEAEs were reported in 76 (13.3%) patients, most common events were blood creatinine increased in 8.8% of patients and renal failure in 3.0% of patients. Thirteen (2.3%) patients had SAEs and 1 patient died due to acute kidney injury. Seven patients discontinued BOSULIF treatment due to an AE related to renal impairment, including two patients who underwent hemodialysis as a result of renal dysfunction. In the phase 3 study in patients newly diagnosed with CP CML treated with bosutinib 400 mg, Renal TEAEs were reported in 19 (7.1%) patients, most common events were blood creatinine increased in 5.6%, acute kidney injury in 0.7 % and Renal Impairment in 0.7%.

The reversibility of the eGFR decline following treatment interruption, dose reduction or treatment discontinuation is unclear, due to limited clinical data.

Monitor patients for renal function at baseline and during therapy with BOSULIF, with particular attention to those patients who have pre-existing renal compromise or risk factors for renal dysfunction (see Special Populations, Renal Impairment, below).

Respiratory

In the clinical studies, 2.3% of patients treated with BOSULIF reported serious respiratory disorders including dyspnoea, pleural effusion, respiratory failure, acute pulmonary edema, pulmonary hypertension, pneumonitis, and interstitial lung disease. In the phase 3 study in patients newly diagnosed with CP CML treated with bosutinib 400 mg, respiratory disorders were reported in 67 (25%) patients with the following Grade 3 or 4 events dyspnoea (0.4%), pneumothorax (0.4%) and respiratory failure (0.4%).

Skin

Stevens-Johnson syndrome has been rarely reported in the post-market setting. Discontinue BOSULIF should this condition be suspected.

Special Populations

***Pregnant Women*:** BOSULIF is teratogenic and is transferred to breast milk. Based on its mechanism of action and findings of embryofetal toxicities in rabbits, BOSULIF can cause fetal harm when administered to a pregnant woman (see TOXICOLOGY). There are no adequate and

well-controlled studies of BOSULIF in pregnant women. If BOSULIF is used during pregnancy, the patient should be advised of the potential serious risks to a developing fetus.

***Nursing Women*:** An animal study demonstrated excretion of bosutinib-derived radioactivity in breast milk. Because many drugs are excreted in human milk and because a potential risk to the nursing infant cannot be excluded, women that are taking BOSULIF should not breast-feed or provide breast milk to infants (see TOXICOLOGY).

***Male Patients*:** There is a potential risk to the developing fetus if exposed to BOSULIF through the semen of male patients, therefore physicians should advise their male patients to use highly effective contraception (including condom) during any sexual contact with females of childbearing potential even if they have undergone a successful vasectomy. The method of contraception should be used while the patient is taking BOSULIF, during interruption of BOSULIF treatment, and for at least 4 weeks after stopping BOSULIF. Physicians should advise their male patients to inform their female sexual partners (with childbearing potential) that they are taking BOSULIF and that there are risks to the developing fetus if exposed to their semen (see DETAILED PHARMACOLOGY).

***Pediatrics (<18 years of age)*:** The safety and efficacy of BOSULIF in patients less than 18 years of age have not been evaluated. No data are available.

***Geriatrics (≥ 65 years of age)*:** The type and frequency of TEAEs of was generally similar between younger (<65 years) vs. older (> 65 years) subjects. The overall frequency of AEs leading to discontinuation was higher in older subjects, however the type of AEs leading to discontinuation was similar.

***Renal Impairment*:** In a renal impairment study, bosutinib exposures were increased in patients with moderate or severe renal impairment. Reduced starting doses are recommended for patients with moderate and severe renal impairment, respectively (see DOSAGE AND ADMINISTRATION, Dosing Considerations, Renal Impairment and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Impairment). The efficacy and safety of BOSULIF were not investigated in these patients, as those with reduced renal function (serum creatinine > 1.5 x ULN) were excluded from the Phase 1/ 2 and Phase 3 BOSULIF CML studies. Initiate BOSULIF therapy in these patients only when perceived benefits outweigh the potential risks. Patients should be closely monitored for renal function at baseline and during therapy (see WARNINGS AND PRECAUTIONS, Renal and Urinary).

Hypertension was reported at a common (8.2%) frequency in patients treated with BOSULIF (see ADVERSE REACTIONS). Patients with renal impairment who are receiving treatment with BOSULIF were at higher risk of developing hypertension. Among patients with renal insufficiency, the frequency of hypertension was greater than for patients without renal insufficiency (13.6% versus 5.8%, respectively).

***Hepatic Impairment*:** Metabolism of bosutinib is mainly hepatic. Clinical studies have excluded patients with ALT and/or AST >2.5 (or >5, if related to disease) x ULN range and/or bilirubin >1.5 x ULN range. BOSULIF should not be used in hepatically impaired patients.

Higher risk of QT prolongation has been seen in patients with declining hepatic function. In a single-oral-dose study, higher bosutinib plasma levels with reduced clearance were reported in non-CML patients with mild, moderate or severe hepatic impairment (Child-Pugh class) at baseline, compared to matching healthy volunteers. Treatment-emergent QTc prolongation was observed in 50% of hepatically impaired patients (including all 6 patients with severe hepatic impairment) versus 11% of healthy volunteers; the frequency, magnitude and duration of QTc prolongation appeared to increase with severity of baseline hepatic impairment (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION, Dosing considerations, ADVERSE REACTIONS and ACTION AND CLINICAL PHARMACOLOGY).

Higher risk of QT prolongation has been seen in patients with declining hepatic function (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY).

Sensitivity/Intolerance: Two cases (less than 0.2%) of Grade 4 drug-related anaphylactic shock were reported in patients treated with BOSULIF (see CONTRAINDICATIONS and ADVERSE REACTIONS).

Leukocytoclastic vasculitis occurred in 1 patient (0.3%). Patients with hypersensitivity to excipients in BOSULIF, such as polyethylene glycol 3350, poloxamer 188, povidone, or other excipients, may be at risk.

***Coagulation Dysfunction/Platelet Disorders*:** Patients with coagulation dysfunction /platelet disorders and who are taking BOSULIF may be at higher risk of bleeding events.

***Serum Lipase / Pancreatitis*:** Elevated serum lipase, amylase and acute pancreatitis have been reported in patients treated with BOSULIF. Patients with previous history of pancreatitis may be at higher risk, so caution is recommended. In cases where lipase elevations are accompanied by abdominal symptoms, BOSULIF should be interrupted and appropriate diagnostic measures considered to rule out pancreatitis.

Monitoring and Laboratory Tests

Patients with Ph+ leukemias should have a complete blood count (including platelet counts) performed weekly for the first month then monthly thereafter, or as clinically indicated (see WARNINGS AND PRECAUTIONS, Hematologic).

Patients should have baseline and monthly liver function tests (including total bilirubin) and renal function tests for the first three months of treatment and periodically thereafter (see WARNINGS AND PRECAUTIONS, Hepatic).

Serum electrolytes (including phosphorus), calcium and magnesium, as well as serum lipase/amylase, should be monitored at baseline and frequently during treatment with BOSULIF, and as clinically indicated. Patients with endocrine abnormalities (e.g. hyperparathyroidism) and/or severe osteoporosis should be monitored closely for changes in bone and mineral

abnormalities, including bone density (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Monitor patients for renal function at baseline and during therapy with BOSULIF, with particular attention to those patients who have pre-existing renal compromise or risk factors for renal dysfunction.

Adequate hydration should be maintained if tumour lysis syndrome is considered a substantial risk.

Patients should be weighed and monitored regularly for fluid retention and managed using standard of care treatment (see WARNINGS AND PRECAUTIONS, Fluid Retention).

Monitoring for an effect on the QTc interval is recommended and a baseline ECG is recommended prior to initiating therapy with BOSULIF and as clinically indicated. Hypokalaemia or hypomagnesaemia must be corrected prior to BOSULIF administration and should be monitored periodically during therapy (see WARNINGS AND PRECAUTIONS, QT/QTc Prolongation).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The safety information provided in this section represents an assessment of the adverse reactions from 1521 patients who received at least 1 oral dose of single-agent BOSULIF in newly diagnosed Ph+ CP CML, CML resistant or intolerant to prior therapy, other Ph+ leukemias, and advanced malignant solid tumors.

Serious adverse reactions reported include anaphylactic shock (see CONTRAINDICATIONS), myelosuppression, gastrointestinal toxicity (diarrhea), fluid retention, hepatotoxicity and rash.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Newly Diagnosed Chronic Phase Ph+ CML

A total of 268 patients newly-diagnosed with CP CML received at least 1 dose of single-agent bosutinib 400 mg in a randomized Phase 3 clinical study. After a minimum of 12 months of follow-up, the median duration of therapy was 14.1 months (range: 0.3 to 24.7 months); the median dose intensity was 391.8 mg/day.

The most frequent adverse reactions reported for ≥20% of patients in the bosutinib treatment group were diarrhoea (70.1% of patients), nausea (35.1%), ALT increased (30.6%), thrombocytopenia (35.1%), abdominal pain (25.3%), and AST increased (22.8%).

The Grade 3 or Grade 4 adverse reactions reported for ≥5% of patients in the bosutinib treatment group were alanine aminotransferase increased (19.0%), lipase increased (9.7%), aspartate aminotransferase increased (9.7%), thrombocytopenia (9.0%), diarrhoea (7.8%), neutropenia (6.0%), and platelet count decreased (5.6%).

Table 1 below presents adverse reactions (all causality) of any toxicity and grades 3/4 very commonly reported (frequencies ≥10%) in the Phase 3 safety population.

Table 1: Newly-Diagnosed CML Patient Receiving BOSULIF 400 mg Reporting Very Common (≥10%) Frequencies Adverse Reactions by All Grades and Grades 3 or 4 for the Phase 3 Safety Population

	Bosutinib 400 mg **Newly Diagnosed Chronic Phase CML** N=268		Imatinib 400 mg **Chronic Phase CML** N=265	
System Organ Class Preferred Term	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
Any Adverse Events	96	51	93	36
Blood and lymphatic system disorders				
Thrombocytopenia	35	14	20	6
Anemia	19	3	19	5
Neutropenia	11	7	21	12
Gastrointestinal disorders				
Diarrhea	70	8	34	<1
Nausea	35	0	38	0
Abdominal pain	25	2	15	<1
Vomiting	18	1	16	0
General disorders and administration site conditions				
Fatigue	19	<1	19	0
Pyrexia	13	<1	8	0
Asthenia	11	0	6	0
Infections and infestations				
Respiratory tract infection	12	<1	12	<1
Investigations				
ALT increased	31	19	6	2
AST increased	23	10	6	2
Lipase increased	13	10	8	5
Metabolism and nutrition disorders				
Appetite decreased	10	<1	6	0
Musculoskeletal and connective tissue disorders				
Arthralgia	11	<1	13	0

Table 1: Newly-Diagnosed CML Patient Receiving BOSULIF 400 mg Reporting Very Common (≥10%) Frequencies Adverse Reactions by All Grades and Grades 3 or 4 for the Phase 3 Safety Population

	Bosutinib 400 mg **Newly Diagnosed Chronic Phase CML** N=268		Imatinib 400 mg **Chronic Phase CML** N=265	
System Organ Class Preferred Term	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
Nervous system disorders				
Headache	19	1	13	1
Skin and subcutaneous disorders				
Rash	26	1	18	2

Note: Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities
Abbreviations: CML=Chronic myelogenous leukemia; N=number of patients.
Thrombocytopenia includes the following preferred terms: Platelet count decreased, Thrombocytopenia.
Anemia includes the following preferred terms: Anemia, Hemoglobin decreased.
Neutropenia includes the following preferred terms: Neutropenia, Neutrophil count decreased.
Abdominal pain includes the following preferred terms: Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness, Gastrointestinal pain.
Fatigue includes the following preferred terms: Fatigue, Malaise.
Respiratory tract infection includes the following preferred terms: Lower respiratory tract infection, Respiratory tract infection, Respiratory tract infection viral, Upper respiratory tract infection, Viral upper respiratory tract infection.
Lipase increased includes the following preferred terms: Hyperlipasaemia, Lipase increased
Rash includes the following preferred terms: Rash, Rash generalized, Rash macular, Rash maculo-papular, Rash papular, Rash pruritic.

Table 2 below presents adverse reactions (all causality) of any toxicity and grades 3/4 commonly reported (frequencies ≥ 1% to <10%) in the Phase 3 safety population.

Table 2: Newly-Diagnosed CML Patient Receiving BOSULIF 400 mg Reporting Common (≥ 1% to <10%) Frequencies Adverse Reactions by All Grades and Grades 3 or 4 for the Phase 3 Safety Population

	Bosutinib 400 mg **Newly Diagnosed Chronic Phase CML** N=268		Imatinib 400 mg **Newly Diagnosed Chronic Phase CML** N=265	
System Organ Class Preferred Term	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
Any Adverse Events	96	51	93	36
Blood and lymphatic system disorders				
Leukopenia	6	1	11	3
Ear and labyrinth disorders				
Tinnitus	2	0	<1	0
Gastrointestinal disorders				
Gastritis	1	0	1	<1
General disorders and administration site conditions				
Oedema	6	0	17	<1
Chest Pain	3	0	3	0
Pain	1	0	3	0
Hepatobiliary disorders				
Hepatic function abnormal	3	2	1	1
Hepatotoxicity	3	2	<1	0
Infections and infestations				
Nasopharyngitis	10	<1	9	0
Bronchitis	3	0	2	<1
Influenza	3	0	3	<1
Pneumonia	3	<1	2	<1
Investigations				
Blood bilirubin increased	6	<1	3	<1
Blood creatinine increased	6	0	6	<1
Amylase increased	5	1	3	1
Blood creatine phosphokinase increased	3	<1	8	2
Gamma-glutamyl transferase increased	2	<1	<1	<1
Electrocardiogram QT prolonged	1	<1	3	<1
Metabolism and nutrition disorders				
Hypophosphataemia	2	<1	6	3
Hyperkalaemia	1	<1	2	0
Musculoskeletal and connective tissue disorders				
Back pain	8	<1	7	<1
Myalgia	3	<1	15	1

Table 2: Newly-Diagnosed CML Patient Receiving BOSULIF 400 mg Reporting Common (≥ 1% to <10%) Frequencies Adverse Reactions by All Grades and Grades 3 or 4 for the Phase 3 Safety Population

	Bosutinib 400 mg **Newly Diagnosed Chronic Phase CML** N=268		Imatinib 400 mg **Newly Diagnosed Chronic Phase CML** N=265	
System Organ Class Preferred Term	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
Nervous system disorders				
Dizziness	7	0	7	0
Dysgeusia	1	0	3	0
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	9	<1	4	<1
Cough	8	0	7	0
Pleural effusion	2	0	2	0
Skin and subcutaneous disorders				
Pruritus	9	0	2	0
Acne	2	0	0	0
Urticaria	2	0	1	0
Vascular disorders				
Hypertension	5	2	6	2

Note: Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities
Abbreviations: CML=Chronic myelogenous leukemia; N=number of patients.
Totals for the No. of Subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report two or more different adverse events within the higher level category. SOC for some preferred terms does not follow MedDRA classification.
The commonality stratification is based on 'All Grade' under Total column.
'Grade 3', 'Grade 4' columns indicate maximum toxicity.
Amylase increased includes the following preferred terms: Amylase increased, Hyperamylasaemia.
Blood bilirubin increased includes the following preferred terms: Blood bilirubin increased, Hyperbilirubinaemia.
Chest pain includes the following preferred terms: Chest discomfort, Chest pain
Electrocardiogram QT prolonged includes the following MedDRA SMQ: Torsade de pointes/QT prolongation (Narrow)
Hepatic function abnormal includes the following preferred terms: Hepatic function abnormal, Hyper transaminasaemia, Liver function test abnormal, Liver function test increased, Transaminases increased
Hepatotoxicity includes the following preferred terms: Hepatitis, Hepatitis acute, Hepatitis cholestatic, Hepatitis toxic,Hepatotoxicity, Liver disorder
Hyperkalaemia includes the following preferred terms: Blood potassium increased, Hyperkalaemia
Hypertension* includes the following high level term and preferred terms: HLT- Accelerated and malignant hypertension, PT- Bloodpressure ambulatory increased, Blood pressure diastolic increased, Blood pressure increased, Blood pressure systolic increased, Diastolic Hypertension, Essential Hypertension, Hypertension, LabileHypertension, Systolic Hypertension
Hypophosphataemia includes the following preferred terms: Blood phosphorus decreased, Hypophosphataemia
Leukopenia includes the following preferred terms: Leukopenia, White blood cell count decreased
Oedema includes the following preferred terms: Face oedema, Localised Oedema, Oedema, Oedema peripheral
Pneumonia includes the following preferred terms: Atypical pneumonia, Pneumonia

In the phase 3 study in patients newly diagnosed with CP CML treated with bosutinib 400 mg, the median time of onset for diarrhea (all grades) in the bosutinib treatment group was 3 days, and the median duration of an event was 3 days. The median time of onset for either ALT or AST elevations (all grades) observed was 32 and 43 days, respectively, and the median duration was 20 and 15 days, respectively.

Chronic Phase (CP), Accelerated Phase (AP) and Blast Phase (BP) CML and ALL Patients Resistant or Intolerant to Previous TKIs Treatment

The single-arm Phase 1/2 clinical study enrolled a total of 571 patients with Ph+ chronic (n=284), accelerated (n=79), or blast (n=64) phase chronic myelogenous leukemia (CML) and 24 patients with Ph+ acute lymphoblastic leukemia (ALL) who were resistant or intolerant to prior TKI therapy. The safety population (received at least 1 dose of BOSULIF) included 570 patients.

With the ≥ 4 years of follow up, the majority of BOSULIF-treated patients (99.5%) experienced at least one adverse event. The most common (incidence ≥ 30%) were diarrhea (81.6%), nausea (47.0%), thrombocytopenia (41.4%), vomiting (39.1%), abdominal pain (38.4%), rash (32.8%), and anemia (30.2%).

Overall, 77.9% of patients experienced severe, Grade 3 and 4 adverse events, and 44.2% of patients experienced serious adverse events (SAEs). The most common SAEs (>2% of subjects overall) were pneumonia (4.9%), pleural effusion (4.7%), pyrexia (3.3%), thrombocytopenia (2.5%), dyspnea (2.3%), disease progression, and diarrhea (2.1% each).

Overall, 134 (24%) of patients permanently discontinued bosutinib due to treatment-emerged adverse events (TEAEs). The most common TEAEs leading to discontinuation (≥ 2% of subjects overall) were thrombocytopenia (5.3%) and ALT increased (2.1%). Overall, 65.3% of subjects had at least one dose interruption due to adverse events. The most common TEAEs (≥ 4% of subjects) resulting in dose interruption were thrombocytopenia (21.6%), diarrhea (11.6%), rash (9.8%), neutropenia (8.1%), vomiting and pleural effusion (6.0% each), ALT increased (7.0%), AST increased (5.1%), and anemia (4.2%). Overall, 49% of subjects had ≥1 dose reduction due to TEAEs. The most common TEAEs (≥ 4% of subjects) resulting in reductions in bosutinib dose were thrombocytopenia (13.5%), rash (5.4%), and diarrhea (4.7%).

Table 3 below presents adverse reactions (all causality) of any toxicity and grades 3/4 very commonly reported (frequencies ≥10%) in the Phase 1/2 safety population.

Table 3: CML Patients Receiving BOSULIF Reporting Very Common (≥10%) Frequencies Adverse Reactions by All Grades and Grades 3 or 4 for the Phase 1/2 Safety Population

	CP* CML Imatinib Resistant or Intolerant N=284		**CP* CML** Resistant or Intolerant ≥2 TKIs N=119		**AP* CML** Resistant or Intolerant to at least Imatinib N=79		**BP* CML** Resistant or Intolerant to at least Imatinib N=64	
System Organ Class Preferred Term	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
Any Adverse Event	100	69	100	61	100	82	97	70
Blood and lymphatic system disorders								
Thrombocytopenia	42	25	38	26	53	44	34	33
Anaemia	29	13	20	7	46	33	30	20
Neutropenia	16	10	21	16	19	18	25	23
Leukopenia	13	5	4	<1	13	6	19	19
Gastrointestinal disorders								
Diarrhoea	86	10	83	9	85	4	64	5
Nausea	46	2	48	<1	46	3	50	2
Abdominal pain	45	2	36	<1	34	5	27	8
Vomiting	37	4	38	<1	44	4	41	3
General disorders and administration site conditions								
Pyrexia	27	1	15	0	35	1	39	3
Fatigue	27	2	23	2	22	5	20	5
Oedema	15	<1	13	0	14	0	14	2
Asthenia	15	2	8	0	14	1	6	0
Chest pain	8	2	6	0	15	3	8	0
Infections and infestations								
Respiratory tract infection	14	<1	15	<1	15	0	5	0
Nasopharyngitis	13	0	11	0	9	0	2	0
Influenza	10	<1	10	0	6	0	0	0
Pneumonia	5	4	4	0	14	11	16	9
Investigations								
ALT increased	22	8	15	6	14	8	6	2
AST decreased	20	4	8	3	15	5	6	0
Blood creatinine increased	9	<1	13	0	8	1	5	0
Metabolism and nutrition disorders								
Decreased appetite	15	<1	13	<1	9	0	19	0
Musculoskeletal and connective tissue disorders								
Arthralgia	17	1	18	<1	15	0	13	0
Back pain	13	<1	12	3	10	1	6	2
Nervous system disorders								
Headache	19	0	27	3	15	3	20	6
Dizziness	9	0	15	0	14	1	13	0

Table 3: CML Patients Receiving BOSULIF Reporting Very Common (≥10%) Frequencies Adverse Reactions by All Grades and Grades 3 or 4 for the Phase 1/2 Safety Population

	CP* CML Imatinib Resistant or Intolerant N=284		**CP* CML** Resistant or Intolerant ≥2 TKIs N=119		**AP* CML** Resistant or Intolerant to at least Imatinib N=79		**BP* CML** Resistant or Intolerant to at least Imatinib N=64	
System Organ Class Preferred Term	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
Respiratory, thoracic and mediastinal disorders								
Cough	23	0	21	0	30	0	13	0
Dyspnoea	12	2	12	2	20	9	19	3
Pleural effusion	11	3	17	5	13	5	5	3
Skin and subcutaneous disorders								
Rash	37	9	30	4	35	4	31	5
Pruritus	10	<1	17	<1	8	0	6	0

* CP = Chronic Phase; AP = Accelerated Phase; BP = Blast Phase

(a)Totals for the No. of Subjects at a higher level are not necessarily the sum of those at the lower levels since asubject may report two or more different adverse events within the higher level category. SOC for some preferred terms does not follow Meddra classification.

Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).

The commonality stratification is based on 'All Grade' under Total column.

'Grade 3', 'Grade 4' column indicate maximum toxicity.

Abdominal pain includes the following preferred terms: Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness, Gastrointestinal pain.

Anaemia includes the following preferred terms: Anaemia, Haemoglobin decreased.

Chest pain includes the following preferred terms: Chest discomfort, Chest pain.

Fatigue includes the following preferred terms: Fatigue, Malaise.

Leukopenia includes the following preferred terms: Leukopenia, White blood cell count decreased.

Neutropenia includes the following preferred terms: Neutropenia, Neutrophil count decreased.

Oedema includes the following preferred terms: Face oedema, Localised Oedema, Oedema, Oedema peripheral.

Rash includes the following preferred terms: Rash, Rash generalised, Rash macular, Rash maculo-papular, , Rash pruritic.

Thrombocytopenia includes the following preferred terms: Platelet count decreased, Thrombocytopenia.

Table 4 below presents adverse reactions (all causality) of any toxicity and grades 3/4 commonly reported (frequencies ≥ 1% to <10%) in the Phase 1/2 safety population.

Table 4: CML Patients Receiving BOSULIF Reporting Common (≥ 1% to <10%) Frequencies Adverse Reactions by All Grades and Grades 3 or 4 for the Phase 1/2 Safety Population

	CP* CML Imatinib Resistant or Intolerant N=284		**CP* CML** Resistant or Intolerant ≥2 TKIs N=119		**AP* CML** Resistant or Intolerant to at least Imatinib N=79		**BP* CML** Resistant or Intolerant to at least Imatinib N=64	
System Organ Class Preferred Term	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
Any Adverse Event	100	69	100	61	100	82	97	70
Blood and lymphatic system disorders								
Febrile Neutropenia	0	0	2	2	1	1	5	3
Cardiac disorders								
Pericardial effusion	3	1	6	3	6	1	2	0
Pericarditis	<1	0	<1	<1	1	1	0	0
Ear and labyrinth disorders								
Tinnitus	1	0	3	0	0	0	0	0
Gastrointestinal disorders								
Gastritis	4	<1	3	<1	4	0	3	2
Gastrointestinal haemorrhage	2	<1	3	0	1	1	5	3
Acute pancreatitis	1	1	0	0	3	3	0	0
General disorders and administration site conditions								
Pain	7	<1	6	0	8	1	8	3
Hepatobiliary disorders								
Hepatotoxicity	4	1	3	3	0	0	3	0
Hepatic function abnormal	3	2	2	0	1	0	3	0
Immune system disorders								
Drug hypersensitivity	<1	<1	4	2	1	0	2	0
Infections and infestations								
Bronchitis	6	<1	5.0	<1	8	0	0	0
Investigations								
Lipase increased	10	7	7	4	8	2.5	5	3
Amylase increased	5	2	5	0	1	0	5	2
Blood creatine phosphokinase increased	5	2	2	0	4	0	0	0
Blood bilirubin increased	4	0	2	<1	3	0	9	8
Gamma-glutamyl transferase increased	2	<1	3	<1	3	0	0	0
Electrocardiogram QT prolonged	1	<1	0	0	0	0	2	0
Metabolism and nutrition disorders								
Hypophosphataemia	6	2	4	0	6	4	6	3
Hyperkalaemia	3	1	5	<1	5	1	5	0
Dehydration	2	0	2	0	4	1	6	0

Table 4: CML Patients Receiving BOSULIF Reporting Common (≥ 1% to <10%) Frequencies Adverse Reactions by All Grades and Grades 3 or 4 for the Phase 1/2 Safety Population

	CP* CML Imatinib Resistant or Intolerant N=284		**CP* CML** Resistant or Intolerant ≥2 TKIs N=119		**AP* CML** Resistant or Intolerant to at least Imatinib N=79		**BP* CML** Resistant or Intolerant to at least Imatinib N=64	
System Organ Class Preferred Term	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
Musculoskeletal and connective tissue disorders								
Myalgia	8	0	4	<1	9	0	9	2
Nervous system disorders								
Dysgeusia	2	0	3	0	3	0	2	0
Renal and urinary disorders								
Renal failure	2	<1	3	2	6	0	2	2
Acute kidney injury	2	1	0	0	1	1	5	3
Renal impairment	2	<1	0	0	1	0	0	0
Respiratory, thoracic and mediastinal disorders								
Pulmonary hypertension	1	<1	<1	0	0	0	0	0
Respiratory failure	<1	<1	0	0	1	1	5	3
Skin and subcutaneous disorders								
Acne	4	0	<1	0	3	0	2	0
Urticaria	2	0	3	<1	3	0	2	2
Exfoliative rash	1	0	0	0	1	0	0	0
Drug eruption	<1	<1	0	0	3	0	0	0

* CP = Chronic Phase; AP = Accelerated Phase; BP = Blast Phase

Totals for the No. of Subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report two or more different adverse events within the higher level category. SOC for some preferred terms does not follow MedDRA classification.

Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).

The commonality stratification is based on 'All Grade' under Total column.

'Grade 3', 'Grade 4' columns indicate maximum toxicity.

Amylase increased includes the following preferred terms: Amylase increased, Hyperamylasaemia.

Blood bilirubin increased includes the following preferred terms: Blood bilirubin increased, Hyperbilirubinaemia.

Electrocardiogram QT prolonged includes the following Electrocardiogram QT prolonged, Long QT syndrome

Gastrointestinal haemorrhage includes the following preferred terms: Anal haemorrhage, Gastrointestinal haemorrhage, Intestinal haemorrhage, Lower gastrointestinal haemorrhage, Rectal haemorrhage.

Hepatotoxicity includes the following preferred terms:, Hepatitis toxic, Hepatotoxicity, Liver disorder.

Hyperkalaemia includes the following preferred terms: Blood potassium increased, Hyperkalaemia .

Hypophosphataemia includes the following preferred terms: Blood phosphorus decreased, Hypophosphataemia.

Lipase increased includes the following preferred terms: Hyperlipasaemia, Lipase increased.

Pancreatitis acute includes the following preferred terms: Pancreatitis, Pancreatitis acute.

Pneumonia includes the following preferred terms: Atypical pneumonia, Pneumonia.

Respiratory tract infection includes the following preferred terms: Lower respiratory tract infection, Respiratory tract infection, Respiratory tract infection viral, Upper respiratory tract infection, Viral upper respiratory tract infection.

In the single-arm Phase 1/2 clinical study, the median time of onset for diarrhea (all grades) was 2 days and the median duration per event was 2 days. Based on adverse reactions reported, the median time of onset for either ALT or AST (all grades) elevations was 29 and 30 days, respectively, and the median duration for each was 18 days.

ECG Findings

In the Phase 1/ 2 clinical study, 1 patient (0.2%) experienced QTcF (corrected QT by the Fridericia method) intervals of greater than 500 ms. Seven (1.2%) of the patients experienced QTcF increases from baseline exceeding 60 ms. Patients with uncontrolled or significant cardiovascular disease, including QT interval prolongation, at baseline were excluded by protocol criteria from the clinical trials.

In the phase 3 study in patients newly diagnosed with CP CML treated with 400 mg, there was 1 patient in the bosutinib treatment group and 0 patients in the imatinib treatment group who experienced corrected QT by the Fridericia method (QTcF) interval of greater than 500 msec.

In a Phase 3 study of newly diagnosed Ph+ CP CML patients treated with 500 mg, 2 patients (0.8%) experienced QTcF interval greater than 500 ms in the BOSULIF treatment arm. Patients with uncontrolled or significant cardiovascular disease including QT interval prolongation were excluded from enrolling in this clinical study. In this study population, BOSULIF was associated with statistically significant decreases from baseline in heart rate of approximately 4 bpm at months 2 and 3.

Tabulated Summary of Adverse Reactions

The following adverse reactions in Table 5 were reported in patients in pooled clinical studies with BOSULIF. They represent an evaluation of the adverse reaction data from 1521 patients who received at least 1 dose of single-agent BOSULIF in newly diagnosed Ph+ CP CML, CML resistant or intolerant to prior therapy, other Ph+ leukemias, and advanced malignant solid tumors. These adverse reactions are presented by system organ class and by frequency. Frequency categories are defined as: very common (≥10%), common (≥1% to <10%), uncommon (≥0.1% to <1%), rare (≥0.01% to <0.1%), very rare (<0.01%), not known (cannot be estimated from the available data).

Table 5 Adverse Reactions for BOSULIF Pooled Safety (Newly diagnosed Ph+ CP CML, CML resistant or intolerant to prior therapy, other Ph+ leukemias, and advanced malignant solid tumors) N= 1521

Infections and infestations	
Very common	respiratory tract infection (including upper respiratory tract infection, lower respiratory tract infection, viral upper respiratory tract infection, respiratory tract infection viral), nasopharyngitis
Common	pneumonia (including pneumonia, atypical pneumonia), influenza, bronchitis
Blood and lymphatic system disorders	
Very common	thrombocytopenia (including platelet count decreased), anemia (including Hemoglobin decreased), neutropenia (including neutrophil count decreased)
Common	leucopenia (including white blood cell count decreased)
Uncommon	febrile neutropenia, granulocytopenia
Immune system disorders	
Uncommon	anaphylactic shock, drug hypersensitivity
Metabolism and nutrition disorders	
Very common	decreased appetite
Common	hyperkalemia (including blood potassium increased), hypophosphatemia (including blood phosphorus decreased), dehydration
Nervous system disorders	
Very common	headache, dizziness
Common	dysgeusia
Ear and labyrinth disorders	
Common	tinnitus
Cardiac disorders	
Common	pericardial effusion
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	dyspnea
Common	pleural effusion
Uncommon	acute pulmonary edema, respiratory failure, pulmonary hypertension

Table 5 Adverse Reactions for BOSULIF Pooled Safety (Newly diagnosed Ph+ CP CML, CML resistant or intolerant to prior therapy, other Ph+ leukemias, and advanced malignant solid tumors) N= 1521

Gastrointestinal disorders	
Very common	diarrhea, vomiting, abdominal pain (including upper abdominal pain, lower abdominal pain, abdominal discomfort, abdominal tenderness, gastrointestinal pain), nausea
Common	gastritis, gastrointestinal hemorrhage (including anal hemorrhage, gastric hemorrhage, upper gastrointestinal hemorrhage, lower gastrointestinal hemorrhage, rectal hemorrhage)
Uncommon	acute pancreatitis
Hepatobiliary disorders	
Common	hepatotoxicity (including toxic hepatitis, cytolytic hepatitis, liver disorder), abnormal hepatic function (including liver function test abnormal, liver function test increased, transaminsases increased)
Uncommon	liver injury (including drug-induced liver injury)
Skin and subcutaneous tissue disorders	
Very common	rash (including maculopapular rash, pruritic rash, generalized rash, papular rash, macular rash)
Common	urticaria, pruritus, acne
Uncommon	erythema multiforme, exfoliative rash, drug eruption
Musculoskeletal and connective tissue disorders	
Very common	arthralgia, back pain
Common	myalgia
Renal and urinary disorders	
Common	acute renal failure, acute kidney injury, renal failure, renal impairment
General disorders and administration site conditions	
Very common	fatigue (including malaise), pyrexia, edema (including face edema, localized edema, peripheral edema), asthenia
Common	chest pain (including chest discomfort), pain
Investigations	
Very common	increased alanine aminotransferase, increased aspartate aminotransferase, increased lipase (including hyperlipasaemia)
Common	increased blood amylase, increased gamma-glutamyltransferase, increased blood creatine phosphokinase, increased blood bilirubin (including hyperbilirubinemia) , electrocardiogram QT prolonged (including long QT symdrome, ventricular tachycardia) , increased blood creatinine

Note: Preferred Terms shown in parenthesis were grouped to determine a more accurate frequency.

All treatment-emergent adverse events that were reported in BOSULIF pooled clinical studies, regardless of causality and frequency, are listed in Table 6 below.

Abnormal Hematologic and Clinical Chemistry Findings

Table 6 presents potential clinically relevant or severe abnormalities of routine hematological, or biochemistry laboratory values in the study patient population who received at least one dose of BOSULIF in the Phase 1/2 study.

Table 6. Percent of Patients with Potential Clinically Relevant or Severe Grade 3/ 4 Laboratory Test Abnormalities in the Phase 1/2 Clinical Study

	CP* CML Imatinib-Resistant or Intolerant N=284	CP* CML Resistant or Intolerant ≥2 TKIs N=119	AP* CML, BP* CML Resistant or Intolerant to at least Imatinib N=143
Hematology parameters	**%**	**%**	**%**
Platelet Count <50 X 10^9/L	26	26	57
Absolute Neutrophil Count <1 X10^9/L	15	18	38
Hemoglobin (Low) <80 g/L	14	8	38
Biochemistry parameters			
SGPT/ALT >5.0 X ULN	12	8	6
SGOT/AST >5.0 X ULN	5	3	3
Lipase >2 X ULN	12	8	6
Phosphorus (Low) <0.6 mmol/L	9	3	7
Total Bilirubin (High) >3xULN	0	2	3

*CP = Chronic Phase; AP = Accelerated Phase; BP = Blast Phase

Table 7 presents potential clinically relevant or severe abnormalities of routine hematological, or biochemistry laboratory values in the study patient population who received at least one dose of BOSULIF in the Phase 3 study.

Table 7. Percent of Patients with Potential Clinically Relevant or Severe Grade 3/ 4 Laboratory Test Abnormalities in the Phase 3 Clinical Study

	Bosutinib 400 mg Newly Diagnosed Chronic Phase CML N=268
Hematology parameters	**%**
Platelet Count <50 X 10^9/L	14
Absolute Neutrophil Count <1 X10^9/L	9
Hemoglobin (Low) <80 g/L	7
Biochemistry parameters	
SGPT/ALT >5.0 X ULN	23
SGOT/AST >5.0 X ULN	12
Lipase >2 X ULN	13
Phosphorus (Low) <0.6 mmol/L	4.5
Total Bilirubin (High) >3xULN	1

Table 8 presents the median (90% CI) change in eGFR from baseline over time in patients with a baseline creatinine value in the Phase 1/2 study (see CLINICAL TRIALS).

Table 8: On-treatment eGFR Change from Baseline Over Time In Patients in the Phase 1/2 study

Time Point (months)	Total (N=569)	eGRF (mL/min/1.73 m^2) Median Change (90% CI)
Baseline	569	NA
3	429	-5.29 (-6.26, -4.02)
12	290	-7.55 (-8.29, -4.89)
24	210	-8.54 (-10.07, -6.55)
36	185	-10.92 (-12.92, -8.62)
48	167	-10.51 (-13.57, -9.20)

Table 9 presents the median (90% CI) change in eGFR from baseline over time in patients with a baseline creatinine value in the Phase 3 study (see CLINICAL TRIALS).

Table 9: On-treatment eGFR Change from Baseline Over Time In Patients in the Phase 3 study

Time Point (months)	Total (N=268)	eGRF (mL/min/1.73 m^2) Median Change (95% CI)
Baseline	267	NA
3	247	-4.9 (-6.9, -2.4)
12	216	-11.1 (-12.9, -9.2)

DRUG INTERACTIONS

Serious Drug and Drug-Food Interactions

- Strong and moderate CYP3A inhibitors increase BOSULIF exposure. Avoid concomitant use of these inhibitors.
- Strong and moderate CYP3A inducers decrease BOSULIF exposure. Avoid concomitant use of these inducers.

Overview

In vitro studies with human liver microsomes indicated that the major CYP450 isozyme involved in the metabolism of bosutinib is CYP3A4. No metabolism of bosutinib was observed with CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A5. Flavin-containing monooxygenase enzymes (FMO1, FMO3, and FMO5) are capable of metabolizing bosutinib to its N-oxide metabolite.

Drug-Drug Interactions

Drugs That May Increase Bosutinib Plasma Concentrations

CYP3A inhibitors: Avoid the concomitant use of strong CYP3A inhibitors (e.g., including but not limited to boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, troleandomycin, voriconazole), or moderate CYP3A inhibitors (e.g., including but not limited to amprenavir, aprepitant, atazanavir,cimetidine, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil, grapefruit products including star fruit, pomegranate, Seville oranges and other similar fruits that are known to inhibit CYP3A4) with BOSULIF, as an increase in bosutinib plasma concentration is possible.

Use caution if mild CYP3A inhibitors are used concomitantly with BOSULIF.

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

In a study of 24 healthy subjects in which five daily doses of 400 mg ketoconazole (a strong CYP3A inhibitor) were co-administered with a single dose of 100 mg of BOSULIF, ketoconazole increased BOSULIF C_{max} by 5.2 (90% CI: [4.3, 6.2])-fold, and BOSULIF AUC in plasma by 8.6 (90% CI: [7.5, 9.9])-fold, as compared with administration of BOSULIF alone under fasting conditions.

In a study of 20 healthy subjects in which a single dose of 125 mg aprepitant (a moderate CYP3A inhibitor) was co-administered with a single dose of 500 mg BOSULIF, aprepitant increased bosutinib C_{max} by 1.5 (90% CI= 1.3 to 1.8)-fold, and bosutinib AUC in plasma by 2.0 (90% CI = 1.7 to 2.4)-fold over a 5-day pharmacokinetic assessment period, as compared with administration of BOSULIF alone under fed conditions.

In vitro transporter studies demonstrated that bosutinib is a substrate for efflux transporters P-gp, BCRP and MRPs. Possible interactions with BOSULIF and concomitant drug efflux transporter inhibitors may occur.

Drugs That May Decrease Bosutinib Plasma Concentrations

CYP3A Inducers: Avoid the concomitant use of strong CYP3A inducers (e.g., including but not limited to carbamazepine, phenytoin, rifampin, St. John's wort or moderate CYP3A inducers (e.g., including but not limited to bosentan, efavirenz, etravirine, modafinil, nafcillin) with BOSULIF.

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

Use caution if mild CYP3A inducers are used concomitantly with BOSULIF.

Following concomitant administration of a single dose of 500 mg of BOSULIF with six daily doses of 600 mg of rifampin in 24 healthy subjects, bosutinib exposure (C_{max} and AUC in plasma) decreased to 14% (90%CI: [12.0, 16.0]) and to 6% (90%CI: [5.0, 7.0]), respectively, of the values when 500 mg of BOSULIF was administered alone in the fed state.

Proton Pump Inhibitors: Use caution when administering BOSULIF concomitantly with proton pump inhibitors (PPIs). Short-acting antacids should be considered as an alternative to PPIs, administration times of BOSULIF and antacids should be separated (e.g take BOSULIF in the morning, and antacids in the evening) whenever possible. BOSULIF displays pH-dependent aqueous solubility *in vitro.* When a single-oral dose of 400 mg of BOSULIF was co-administered with multiple-oral doses of 60 mg of lansoprazole (a PPI) in a study of 24 healthy fasting subjects, bosutinib C_{max} and AUC decreased to 54% (90%CI: [42.0, 70.0]) and 74% (90%CI: [60.0, 90.0]), respectively, of the values seen when 400 mg of BOSULIF was given alone.

Drugs That May Have Their Plasma Concentration Altered By Bosutinib

Substrates of CYP: An *in vitro* study indicates that clinical drug-drug interactions are unlikely to occur as a result of induction by BOSULIF on the metabolism of drugs that are substrates for CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A4.

In vitro, bosutinib inhibited CYP2C19, CYP2D6, and CYP3A4/5 at concentrations that were 26- to 71-fold higher than the C_{max} in humans at 500 mg once daily.

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)1, and OCT2 at clinically relevant concentrations, but may have the potential to inhibit BCRP in the gastrointestinal tract and OCT1.

Anti-arrhythmic Medicines and Other Drugs That May Prolong QT:

Concomitant use of BOSULIF with another QT/QTc-prolonging drug is discouraged. Drugs that have been associated with QT/QTc interval prolongation and/or torsade de pointes include, but are not limited to, the examples in the following list. Chemical/pharmacological classes are listed if some, although not necessarily all, class members have been implicated in QT/QTc prolongation and/or torsade de pointes:

- Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide);
- Class III antiarrhythmics (e.g., amiodarone, sotalol, dronedarone, ibutilide);
- Class 1C antiarrhythmics (e.g., flecainide, propafenone);
- antipsychotics (e.g., chlorpromazine, pimozide, haloperidol, droperidol, ziprasidone);
- antidepressants (e.g., fluoxetine, citalopram, venlafaxine, tricyclic/tetracyclic antidepressants e.g., amitriptyline, imipramine, maprotiline);
- opioids (e.g., methadone);
- macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin, telithromycin, tacrolimus);
- quinolone antibiotics (e.g., moxifloxacin, levofloxacin, ciprofloxacin);
- antimalarials (e.g., quinine, chloroquine);
- azole antifungals (e.g., ketoconazole, fluconazole, voriconazole);
- domperidone;
- 5-hydroxytryptamine (5-HT)3 receptor antagonists (e.g., dolasetron, ondansetron);
- tyrosine kinase inhibitors (e.g., vandetanib, sunitinib, nilotinib, lapatinib);
- histone deacetylase inhibitors (e.g., vorinostat);
- beta-2 adrenoceptor agonists (e.g., salmeterol, formoterol). (See Warnings and Precautions, Cardiovascular, Action and Clinical Pharmacoogy, QT/QTc Prolongation)

The use of BOSULIF* is discouraged with drugs that can disrupt electrolyte levels, including, but not limited to, the following:

- loop, thiazide, and related diuretics;
- laxatives and enemas;

• amphotericin B;
• high dose corticosteroids.

The above lists of potentially interacting drugs are not comprehensive. Current information sources should be consulted for newly approved drugs that prolong the QT/QTc interval, inhibit metabolizing enzymes and/or transporters, or cause electrolyte disturbances, as well as for older drugs for which these effects have recently been established.

Drug-Food Interactions

Administration of BOSULIF with a meal increased BOSULIF C_{max} 1.8- fold and AUC 1.7-fold, respectively at the dose of 400 mg in healthy subjects (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption and Special Populations). BOSULIF taken without a meal may decrease BOSULIF's bioavailability.

Products and juices containing grapefruit, star fruit, pomegranate, Seville oranges and other similar fruits that are known to inhibit CYP3A4, should be avoided at any time as they may increase BOSULIF plasma concentrations.

Drug-Herb Interactions

St. John's Wort is a strong CYP3A4 inducer. Avoid the concomitant use of strong CYP3A inducers with BOSULIF as this may lead to decreased plasma concentrations of BOSULIF (see DRUG INTERACTIONS, Drug-Drug Interaction and DOSAGE AND ADMINISTRATION).

Drug-Laboratory Test Interactions

Interactions between BOSULIF and laboratory tests have not been studied.

Drug-Lifestyle Interactions

Effects on ability to drive and use machinery
No studies on the effects of bosutinib on the ability to drive and operate machines have been performed. Patients experiencing dizziness or other undesirable effects with a potential impact on the ability to safely drive or use machines should refrain from these activities as long as these undesirable effects persist (see ADVERSE REACTIONS).

Alcohol
No studies have been performed on the potential interaction between bosutinib and alcohol consumption.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Bosutinib should be taken orally once daily, swallowed whole, with a meal. Patients should take their dose of bosutinib at approximately the same time each day. Do not take with grapefruit

products and star fruit, pomegranate, Seville oranges and other similar fruits that are known to inhibit CYP3A4 (see DRUG INTERACTIONS, Serious Drug and Drug-Food Interactions). Tablets should not be crushed or cut, and should not be dissolved in a liquid.

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

If a patient misses a dose (delayed by more than 12 hours), the patient should not take a dose that day, but take the usual prescribed dose on the following day.

In clinical studies of adult Ph+ CML patients, dose escalation by increments of 100 mg once daily to a maximum of 600 mg once daily was allowed in patients who did not achieve a hematologic, cytogenetic, or molecular response and who did not have Grade 3 or higher adverse reactions at the recommended starting dosage. Dose escalations are expected to result in greater toxicity.

Newly-diagnosed chronic phase Ph+ CML

The recommended dose of BOSULIF is 400 mg orally once daily swallowed whole with a meal.

Chronic, accelerated, or blast phase Ph+ CML with resistance or intolerance to prior therapy

The recommended dose and schedule of BOSULIF is 500 mg orally once daily swallowed whole, with a meal.

Dose Adjustments for Non-Hematologic Adverse Reactions
Elevated liver transaminases: If elevations in liver transaminases >5 x institutional upper limit of normal (ULN) occur, BOSULIF should be interrupted until recovery to ≤2.5 x ULN and may be resumed at 400 mg once daily thereafter. If recovery takes longer than 4 weeks, discontinuation of BOSULIF should be considered. If transaminase elevations ≥3 x ULN occur concurrently with bilirubin elevations >2 x ULN and alkaline phosphatase <2 x ULN, BOSULIF should be discontinued.

Diarrhea: For NCI CTCAE Grade 3-4 diarrhea (increase of ≥7 stools/day over baseline/pretreatment), BOSULIF should be interrupted temporarily. Patients with these events should be managed using standard of care treatment, including antidiarrheal medication, and/or fluid replacement. BOSULIF may be resumed at a dose reduced by 100 mg taken once daily upon recovery to grade ≤1.

If other clinically significant moderate or severe non-hematological toxicity develops, BOSULIF 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 of the dose to the starting dose taken once daily may be considered. Doses less than 300 mg/day have been used in patients; however, efficacy has not been established.

Dose Adjustments for Hematologic Adverse Reactions
Dose reductions are recommended for severe or persistent neutropenia and thrombocytopenia as described below. Dose interruptions and/or reductions may be needed for hematologic toxicities (neutropenia, thrombocytopenia) that are not related to underlying leukemia (Table 10).

Table 10: Dose Adjustments for Neutropenia and Thrombocytopenia

Absolute Neutrophil Count ANC[a] $<1.0x10^9$/L or Platelets $<50x10^9$/L	Hold BOSULIF until ANC $\geq 1.0x10^9$/L and platelets $\geq 50x10^9$/L. Resume treatment with BOSULIF 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 either of these cytopenias recurs, reduce dose by an additional 100 mg upon recovery and resume treatment. Doses less than 300 mg/day have been used in patients; however, efficacy has not been established.

Dosing Considerations

Concomitant Use With CYP3A Inhibitors
Avoid the concomitant use of strong or moderate CYP3A inhibitors with BOSULIF as an increase in bosutinib plasma concentration is possible (see DRUG INTERACTIONS, Serious Drug and Drug-Food Interactions).

Concomitant Use With CYP3A Inducers
Avoid the concomitant use of strong or moderate CYP3A with BOSULIF. Based on the large reduction in bosutinib exposure that occurred when BOSULIF was co-administered with rifampin, increasing the dose of BOSULIF when co-administering with strong or moderate CYP3A inducers is unlikely to sufficiently compensate for the loss of exposure (see DRUG INTERACTIONS, Drug-Drug Interactions).

Hepatic Impairment
BOSULIF is contraindicated in patients with hepatic impairment at baseline. (see CONTRAINDICATIONS and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Hepatic Impairment).

Renal Impairment

Newly-diagnosed chronic phase 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 WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Impairment).

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 WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Impairment).

Chronic, accelerated, or blast phase Ph+ CML with resistance or intolerance to prior therapy

In patients with moderate renal impairment [creatinine clearance (CrCL) 30 to 50 mL/min, estimated by the Cockcroft-Gault formula], the recommended dose of bosutinib is 400 mg daily with food (see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Impairment).

In patients with severe renal impairment (CrCL <30 mL/min, estimated by the Cockcroft-Gault formula), the recommended dose of bosutinib is 300 mg daily with food (see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Impairment).

The starting dose recommendation in patients with moderate or severe renal impairment was based on pharmacological modeling; the efficacy and safety of BOSULIF have not been investigated in these patients. Initiate BOSULIF therapy in these patients only when perceived benefits outweigh the potential risks. Patients should be closely monitored for renal function at baseline and during therapy (see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Impairment).

Missed Dose

If a dose is missed (delayed by more than 12 hours), the patient should not take a dose that day, but take the usual prescribed dose on the following day.

Administration

For oral use.

OVERDOSAGE

Experience with BOSULIF overdose in clinical studies was limited to isolated cases. There were no reports of any serious adverse events associated with the overdoses. Patients who take an overdose of BOSULIF should be observed and given appropriate supportive treatment.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

BOSULIF belongs to a pharmacologic class of drugs known as tyrosine kinase inhibitors. BOSULIF inhibits the activity of the oncogenic Bcr-Abl kinase that promotes CML, and Src-family of kinases such as Src, Lyn and Hck, which participate in Bcr-Abl signaling. Modeling studies indicate that BOSULIF binds the kinase domain of Bcr-Abl. BOSULIF also inhibits other kinases such as EPH, TEC and STE20 kinases. BOSULIF minimally inhibits platelet-derived growth factor (PDGF) receptor and c-Kit (protein-tyrosine kinase Kit).

BOSULIF exhibits potent anti-leukemic activity in imatinib-sensitive and resistant BCR-ABL-dependent leukemia cells. In *in vitro* studies, BOSULIF inhibits proliferation and survival of established CML cell lines, Ph+ ALL cell lines, and patient-derived primary primitive CML cells. BOSULIF inhibited 16 of 18 imatinib-resistant forms of Bcr-Abl expressed in murine myeloid cell lines, except T315I. Bosutinib treatment reduced the size of CML tumors growing in nude mice and inhibited growth of murine myeloid tumors expressing imatinib-resistant forms of Bcr-Abl. BOSULIF 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.

Pharmacodynamics

QT/QTc Prolongation
The effect of single dose BOSULIF 500 mg administration on corrected QT interval ($QTcF=QT/RR^{0.33}$) was evaluated in a two part study (Part A & Part B).

Part A was a randomized, double-blind (with respect to bosutinib), 3 period crossover in which healthy male subjects (N=58) received single doses of bosutinib 500 mg, placebo, or moxifloxacin 400 mg in the fed state. The maximum observed QTcF difference from placebo during treatment with bosutinib 500 mg was 2.46 msec (90% CI: [0.54, 4.38]) at 8 h. The results for Part A cannot be extrapolated to steady-state use of bosutinib because the maximal plasma concentrations achieved after the single 500 mg dose (mean C_{max} 114±39.8 ng/mL) were only 42-57% of the maximal plasma concentrations observed in the target patient population receiving bosutinib 500 mg at steady-state (mean C_{max} 200-273 ng/mL).

Part B was a randomized, double-blind (with respect to bosutinib), 2 period crossover in which healthy male subjects (N=54) were administered a single dose of test article (bosutinib 500 mg or placebo) concomitantly with ketoconazole in the fed state. On day -1, ketoconazole was administered as a single oral 400 mg dose in each period. On day 1, the subjects received bosutinib 500 mg or placebo concomitantly with 400 mg ketoconazole in the fed state. On days 2 and 3, subjects received single oral doses of 400 mg ketoconazole. Part B did not have a placebo only treatment arm or a drug-free baseline. The maximal mean difference in QTcF interval between ketoconazole plus bosutinib and ketoconazole plus placebo was 7.36 msec (90% CI: [5.09, 9.63]) at 8 h on day 1. The mean C_{max} achieved after a single 500 mg dose of bosutinib in the presence of ketoconazole was 326±77.2 ng/mL.

Patients with hepatic impairment may be at increased risk of developing QT/QTc prolongation. In a single-oral-dose (200 mg) study in non-CML patients, treatment-emergent QTc prolongation was observed in 50% of hepatically impaired patients (Child-Pugh class A, B or C), versus 11% of matching healthy volunteers; the frequency, magnitude and duration of QTc prolongation appeared to increase with severity of hepatic impairment: all 6 patients with Child-Pugh C at baseline had QTc prolongation following treatment, versus 1/6 and 2/6 of patients of Child-Pugh A and B, respectively. Except for one patient who recorded QTc of 450 msec at day 1 predose, all other Child-Pugh C patients (n=5) had QTc prolongation starting 3 hours post-dose lasted from Day 4 and beyond. The greatest relative QTc increase over baseline was 48 msec in one patient with Child-Pugh C hepatic impairment. However, no QTc > 500 msec was reported for any volunteer in the study.

Pharmacokinetics

Table 11. Summary of BOSULIF's Pharmacokinetic Parameters in CML Fed Patients at Steady-state after 15 Consecutive Days of 400, 500 and 600 mg Oral Dose

Dose (mg)	N	C_{max} (ng/mL)	$t_{½}$ (h)	AUC_{0-24} (ng*h/mL)	Clearance (CL/F) (L/h)
400	3	146 (20)	46.0 (32.3)	2720 (442)	150 (23)
500	3	200 (12)	21.7 (4.6)	3650 (425)	138 (17)
600	10	208 (73)	25.9 (24.9)[a]	3630 (1270)[b]	185 (66)[b]

Data are mean *(standard deviation)* values.
a: n = 7
b: n = 9

Absorption: Following administration of a single oral dose of BOSULIF (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 90 (24) ng/mL and the mean AUC was 2060 (448) ng•h/mL after a single dose of bosutinib (400 mg) with food; and the mean standard deviation (SD) C_{max} value was 112 (29) ng/mL, and the mean (SD) AUC was 2740 (790) ng•h/mL after a single dose of bosutinib (500 mg) with food in healthy subjects, respectively.

Food increased bosutinib C_{max} 1.8-fold and bosutinib AUC 1.7-fold compared to the fasting state. The mean (SD) C_{max} value was 146 (20) ng/mL and the mean (SD) AUC_{tau} was 2720 (442) ng•h/mL after 15 daily dosing of bosutinib tablet (400 mg) with food; and the mean (SD) C_{max} value was 200 (12) ng/mL, and the mean (SD) AUC_{tau} was 3650 (425) ng•h/mL after 15 daily dosing of bosutinib tablet (500 mg) with food in patients with CML.

Bosutinib displays pH-dependent aqueous solubility *in vitro.* Lansoprazole decreases bosutinib exposure (see Drug-Drug Interactions).

Distribution: After administration of a single intravenous (IV) dose of BOSULIF 120 mg to healthy subjects, bosutinib had a mean volume of distribution (standard deviation) of 2441 (796) L suggesting that bosutinib is extensively distributed to extra-vascular tissue and/or with low oral bioavailability. In an animal study with rat, bosutinib did not cross the blood-brain barrier.

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

Metabolism: *In vitro* studies with human liver microsomes indicated that the major CYP450 isozyme involved in the metabolism of bosutinib is CYP3A4. No metabolism of bosutinib was observed with CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A5. Flavin-containing monooxygenase enzymes (FMO1, FMO3, and FMO5) are capable of metabolizing bosutinib to its N-oxide metabolite. *In vitro* and *in vivo* studies indicated that bosutinib (parent compound) undergoes predominantly hepatic metabolism (by CYP3A4) in humans. Following administration of single or multiple doses of BOSULIF (400 mg 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 feces, bosutinib and *N*-desmethyl bosutinib were the major drug-related components.

Elimination: In 14 healthy subjects given a single IV dose (120 mg) of bosutinib, the mean (SD) terminal phase elimination half-life ($t_{1/2}$) was 35.5 (8.5) hours, and the mean (SD) clearance (Cl) was 63.6 (14.1) L/h. In six healthy male subjects given a single oral dose of [^{14}C] radiolabeled bosutinib, an average of 94.6% of the total administered radioactivity was recovered in 9 days; feces (91.3% of dose) was the major route of excretion, with 3.29% of the dose recovered in urine. Excretion was rapid, with 75% of the dose recovered within 96 hours. Excretion of unchanged bosutinib in urine was low, approximately 1% of the administered dose, in healthy subjects.

Linearity / Non-linearity: Both observed C_{max} and AUC values of bosutinib increased with increasing dose in a linear fashion when single, ascending oral doses of 200- to 800 mg bosutinib were administered with food to healthy subjects. At steady state (reached in approximately 15 days), C_{max} and AUC values of bosutinib increased in a less than dose proportional manner between 500 and 600 mg taken with food in CML patients in a dose escalation study (see Table 8). The interpretation of bosutinib dose proportionality finding at steady state may be limited by small number of subjects and high interindividual variability. Based on a population pharmacokinetic analysis in cancer patients, bosutinib is predicted to exhibit dose proportional increase over the dose range of 200 -600 mg with food.

OTHER CONSIDERATIONS:

Special Populations and Conditions

Pediatrics *(<18 years of age)*: The safety and efficacy of BOSULIF in patients less than 18 years of age have not been evaluated. No data are available.

Geriatrics (≥ *65 years of age):* No clinically relevant age-related pharmacokinetic differences have been observed in the elderly. No specific dose recommendation is necessary in the elderly.

Hepatic Impairment: Metabolism of bosutinib is mainly hepatic. Clinical studies have excluded patients with ALT and/or AST >2.5 (or >5, if related to disease) x ULN range and/or bilirubin >1.5 x ULN range.

In a single-oral-dose study, BOSULIF (200 mg) 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 $t_{1/2}$ of bosutinib increased 1.6-fold, 2.0-fold and 2.0-fold and CL/F decreased to 45, 50 and 52% in hepatic impaired patients (subjects (Child-Pugh classes A, B, and C) as compared to the healthy subjects (see CONTRAINDICATIONS; WARNINGS AND PRECAUTIONS, Special Populations; DOSAGE AND ADMINISTRATION, Dosing Considerations; ADVERSE REACTIONS and ACTION AND CLINICAL PHARMACOLOGY).

Renal Impairment: In a dedicated renal impairment trial, a single dose of Bosulif 200 mg was administered with food to 26 non-CML subjects with mild, moderate or severe renal impairment and to 8 matching healthy volunteers. Renal impairment was based on CrCl (calculated by 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 % (90%CI: [-1.0, 85.0]) and 60% (90%CI: [16.0, 121.0]), respectively. Bosutinib exposure was not changed in subjects with mild renal impairment. Based on pharmacokinetic linearity, a daily dose of 400 mg in patients with moderate renal impairment and 300 mg in patients with severe renal impairment are predicted to result in an area under the concentration curve (AUC) that are 108% and 96%, respectively of the AUC seen in patients with normal renal function receiving 500 mg daily. The half-life (57, 55 and 57 hours) of bosutinib in subjects with mild, moderate and severe renal impairment was similar to its half-life (54 hours) in healthy subjects. CL/F values of bosutinib in healthy subjects and in subjects with mild, moderate and severe renal impairment were 3021, 2965, 2238 and 1892 mL/min.

STORAGE AND STABILITY

Store at 20°C to 25°C.

SPECIAL HANDLING INSTRUCTIONS

Not Applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

BOSULIF (bosutinib) 100 mg tablets:
Each 100 mg BOSULIF tablet contains 103.40 mg of bosutinib monohydrate, equivalent to 100 mg of bosutinib.
Yellow, oval, biconvex, film-coated tablet debossed with "Pfizer" on one side and "100" on the other.

Non-medicinal ingredients:
Croscarmellose sodium, iron oxide yellow, magnesium stearate, microcrystalline cellulose, poloxamer, polyethylene glycol, polyvinyl alcohol, povidone, talc, and titanium dioxide.

BOSULIF (bosutinib) 400 mg tablets[§]*:*
Each 400 mg BOSULIF tablet contains 413.60 mg of bosutinib monohydrate, equivalent to 400 mg of bosutinib.
Orange, oval, biconvex, film-coated tablet debossed with "Pfizer" on one side and "400" on the other.

Non-medicinal ingredients:
Croscarmellose sodium, iron oxide yellow, iron oxide red, magnesium stearate, microcrystalline cellulose, poloxamer, polyethylene glycol, polyvinyl alcohol, povidone, talc, and titanium dioxide.

BOSULIF (bosutinib) 500 mg tablets:
Each 500 mg BOSULIF tablet contains 516.98 mg of bosutinib monohydrate, equivalent to 500 mg of bosutinib.
Red, oval, biconvex, film-coated tablet debossed with "Pfizer" on one side and "500" on the other.

Non-medicinal ingredients:
Croscarmellose sodium, iron oxide red, magnesium stearate, microcrystalline cellulose, poloxamer, polyethylene glycol, polyvinyl alcohol, povidone, talc, and titanium dioxide.

BOSULIF (bosutinib) tablets are available in the following packaging configurations (Table 12):

Table 12: Tablet Presentations

Tablet Strength (mg)	Package Configuration	Tablet Description
100 mg	120 tablets per bottle	Yellow, oval, biconvex, film-coated tablets, debossed "Pfizer" on one side and "100" on the other.
	28 tablets (2 blister packs* with 14 tablets each)	
400 mg[§]	30 tablets per bottle	Orange, oval, biconvex, film-coated tablets, debossed "Pfizer" on one side and "400" on the other.
	28 tablets (2 blister packs* with 14 tablets each)	
500 mg	30 tablets per bottle	Red, oval, biconvex, film-coated tablets, debossed "Pfizer" on one side and "500" on the other
	28 tablets (2 blister packs* with 14 tablets each)	

*White opaque 3-ply Polyvinyl chloride (PVC)/ACLAR/PVC blisters sealed with push-through foil backing

[§] Not commercially available in Canada

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

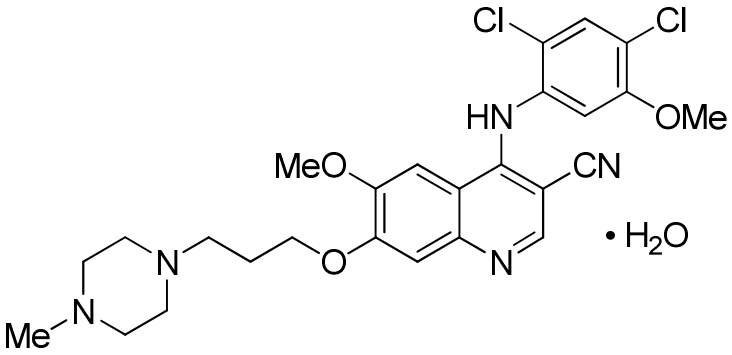
Proper/common name: Bosutinib

Chemical name: 3-Quinolinecarbonitrile, 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(4-methyl-1-piperazinyl)propoxy]-, hydrate (1:1)

Molecular formula: $C_{26}H_{29}Cl_2N_5O_3 \bullet H_20$ (monohydrate)

Molecular mass: 548.46 (monohydrate), equivalent to 530.46 (anhydrous)

Structural formula:



Physicochemical properties: Bosutinib monohydrate is a white to yellowish-tan powder. Bosutinib monohydrate has a pH dependent solubility across the physiological pH range. At or below pH 5, bosutinib behaves as a highly soluble compound. Above pH 5, the solubility of bosutinib reduces rapidly.

CLINICAL TRIALS

Newly-diagnosed CP Ph+ CML

A 2-arm, Phase 3, open-label, multicenter 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 CP Ph+ CML. The trial randomized 536 patients (268 in each treatment group) with Ph+ or Ph- newly-diagnosed CP CML (intent-to-treat [ITT] population) including 487 patients with Ph+ CML harboring b2a2 and/or b3a2 transcripts at baseline, and baseline BCR-ABL copies >0 (modified intent-to-treat [mITT] population).

The mITT population excluded 12 Ph– patients (ie, 0 out of ≥10–99 metaphases at baseline; 6 in each treatment group), 8 patients with atypical transcripts (3 treated with bosutinib and 5 treated with imatinib), and 31 patients with unknown Ph status (13 treated with bosutinib and 18 treated with imatinib, including 2 imatinib-treated patients also listed as having atypical transcripts).

The primary objective was to compare the proportion of patients demonstrating the primary endpoint major molecular response (MMR) at 12 months (48 weeks) in the bosutinib arm compared with that in the imatinib arm in the mITT population. Major molecular response was defined as ≤0.1% BCR-ABL (corresponding to ≥3 log reduction from standardized baseline) with a minimum of 3000 ABL transcripts as assessed by the central laboratory. The secondary efficacy endpoints included MMR by 18 months, duration of MMR, complete cytogenetic response (CCyR) by 12 months, duration of CCyR, event-free survival (EFS), and overall survival (OS). 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. 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 was 52 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%, 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). Baseline characteristics were similar in the ITT population.

After a minimum of 12 months of follow-up in the mITT population, 77.6% of patients treated with bosutinib (N=246) 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 accelerated or blast phase CML for bosutinib-treated patients were 0.8% (2 patients) compared to 1.7% (4 patients) for imatinib-treated patients.

Five bosutinib patients and 7 imatinib patients had CML that transformed to AP CML or BP CML while on treatment.

After a minimum of 12 months of follow-up in the mITT population, discontinuations due to suboptimal response or treatment failure as assessed by the investigator occurred for 2% 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.

There were no on-treatment (up to 28 days after last dose of study drug) or treatment-related deaths in the bosutinib group and 4 on-treatment deaths, including 1 treatment-related death of sepsis, in the imatinib group.

The efficacy results are summarized in Table 13.

Table 13 - Summary of Major Molecular Response (MMR) at Months 12 and 18 and Complete Cytogenetic Response (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, %)	116 (47.2)[a]	89 (36.9)	0.0100[a]
MMR at Month 12 (95% CI)	(40.9, 53.4)	(30.8, 43.0)	
	140 (56.9)	115 (47.7)	0.0208[b]
MMR at Month 18 (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.

The MMR rate at Months 12 and 18 for all randomised subjects (ITT population) was consistent with the mITT population; odds ratio of 1.57 [95% CI: 1.10, 2.22] and 1.50 [95% CI: 1.07, 2.10], respectively.

Chronic Phase (CP), Accelerated Phase (AP) and Blast Phase (BP) Ph+CML and Ph+ALL Patients Resistant or Intolerant to Previous TKIs Treatment

A single-arm, Phase 1/2 open-label, multicenter study was conducted to evaluate the efficacy and safety of BOSULIF 500 mg once daily in patients with imatinib-resistant or -intolerant CML with separate cohorts for chronic, accelerated, and blast phase disease treated with imatinib only or imatinib followed by dasatinib and/or nilotinib. The definition of imatinib resistance included failure to achieve or maintain any hematologic improvement within 4 weeks, or achieve a complete hematologic response (CHR) by 3 months, cytogenetic response (CyR) by 6 months or major cytogenetic response (MCyR) by 12 months or progression of disease after a previous cytogenetic or hematologic response, or presence of a genetic mutation in the BCR-Abl gene associated with imatinib resistance. Imatinib intolerance was defined as inability to tolerate imatinib due to toxicity, or progression on imatinib and inability to receive a higher dose due to toxicity. The definitions of resistance and intolerance to both dasatinib and nilotinib were similar to those for imatinib.

The primary objective of the study was to determine the Major Cytogenetic response (MCyR) rate at Week 24 in patients with imatinib-resistant CP CML who have had imatinib exposure only (primary endpoint analysis cohort). The secondary objectives were to estimate the MCyR rate at Week 24 in patients with imatinib-intolerant CP CML who have had imatinib exposure only, MCyR rate by Week 24 in patients with CP CML previously treated with imatinib who are also resistant to dasatinib or nilotinib or who are intolerant to dasatinib and the Overall Hematologic Response (OHR) by Week 48 for AP CML and BP CML patients who received ≥ 1prior TKIs including imatinib.

In the final analysis (≥ 4 years of follow-up), the key efficacy endpoints included rates of Complete Cytogenetic Response (CCyR), MCyR, OHR; the median time to and the duration of responses; transformation to AP or BP CML, Progression Free Survival (PFS) and Overall Survival (OS).

Table 14 presents the duration of follow-up and treatment with BOSULIF in the final analysis.

Table 14. Duration of Follow-up and Treatment with BOSULIF

	CP CML		**AP CML**	**BP CML**
	Previously Treated with IM N=284	**IM + (D or NI) N=119**	**N=79**	**N=64**
Minimum Time to Database Snapshot, months	60	48	48	48
Median Follow Up, months (range)	43.8 (0.6-96.3)	30.6 (0.3-93.4)	28.1 (0.3-88.6)	10.4 (0.4-79.9)
Median Duration of Treatment, months (range)	25.6 (0.2-96.3)	8.6 (0.2-93.2)	10.2 (0.1-88.6)	2.8 (0.03-61.6)

Abbreviations: D=dasatinib, IM=imatinib, NI=nilotinib,

CP CML previously treated with imatinib only

Table 15. Demographic and Baseline Characteristics of Ph+ CP CML Patients Previously Treated with imatinib only

Characteristic	Imatinib Resistant N=195	Imatinib Intolerant N=89	Total N=284
Sex, n (%)			
Female	82 (42.1)	53 (59.6)	135 (47.5)
Male	113 (57.9)	36 (40.4)	149 (52.5)
Race, n (%)			
Asian	41 (21.0)	21 (23.6)	62 (21.8)
Black	11 (5.6)	5 (5.6)	16 (5.6)
Other[a]	12 (6.2)	8 (9.0)	20 (7)
White	131 (67.2)	55 (61.8)	186 (65.5)
Age category, n (%)			
Age <65 years	159 (81.5)	62 (69.7)	221 (77.8)
Age ≥65 years	36 (18.5)	27 (30.3)	63 (22.2)
ECOG Performance Status, n (%)			
0	151 (77.4)	66 (74.2)	217 (76.4)
1	44 (22.6)	21 (23.6)	65 (22.9)
2	0	1 (1.1)	1
Missing	0	1 (1.1)	1
Number of prior therapies,[b] n (%)			
1	118 (60.5)	66 (74.2)	184 (64.8)
2	77 (39.5)	23 (25.8)	100 (35.2)
Prior interferon therapy, n (%)			
No	118 (60.5)	66 (74.2)	184 (64.8)
Yes	77 (39.5)	23 (25.8)	100 (35.2)
Prior imatinib therapy, n (%)			
Intolerant	0	89 (100)	89 (31.3)
Resistant	195 (100)	0	195 (68.7)
Prior stem cell transplant, n (%)			
No	189 (96.9)	87 (97.8)	276 (97.2)
Yes	6 (3.1)	2 (2.2)	8 (2.8)
Reason for stopping imatinib, n (%)			
Adverse event (intolerance)	0	88 (99)	88 (31)
Disease progression/Inadequate response	195 (100)	0	195 (68.7)
Other[c]	0	1 (1)	1

Abbreviations: ECOG=Eastern Cooperative Oncology Group; N/n=number of subjects
(a) Race Other: Hispanic-15, Mestizo-2, Mixed Race-1, North-African-1.
(b) If a subject received more than 1 treatment regimen with imatinib, dasatinib, nilotinib or interferon the subject is only counted once for the respective treatment.
(c) Other reason for stopping imatinib: Subject wanted to get pregnant.
(d) When the study was initiated, the reason for stopping imatinib and progressive disease date were not part of the data collected; therefore, in the case of these subjects, the data are missing.

Of the 284 patients with CP CML previously treated with imatinib only, 262 patients were evaluable for efficacy.

The efficacy results in the CP CML patients previously treated with imatinib are in Table 16 MCyR was achieved in 66 of 186 evaluable patients (35.7%; 95% CI: [28.8, 43.1]) at Week 24 in the primary endpoint analysis cohort (CP CML imatinib-resistant).

Table 16. Efficacy Results in Ph+ CP CML Patients Previously Treated with Imatinib Only

	Imatinib Resistant (n= 195)	Imatinib Intolerant[b] (n=89)	Total (N=284)
At Week 24			
MCyR	35.7%	30.0%)	34.0%
(95% CI)[a]	(28.8,43.1)	(20.3,41.3)	(28.3,40.1)
CCyR	24.2%	25.0%	24.4%
(95% CI)[a]	(18.2,31.1)	(16.0,35.9)	(19.4,30.1)
Cumulative[c]			
MCyR[a]	58.8%	61.3%	59.5%
(95% CI)[a]	(51.3,66.0)	(49.7,71.9)	(53.3,65.5)
CCyR[a]	48.4%	52.5%	49.6%
(95% CI)[a]	(40.9,55.9)	(41.0,63.8)	(43.4,55.8)
Progression free survival[d]			
KM at year 5,	69.4%	80.9%	72.5%
(95% CI)	(61.2, 76.2)	(66.7, 89.4)	(65.6, 78.2)
Overall survival[d]			
KM at year 5,	80.6%	88.4%	83.1%
(95% CI)	(73.6, 85.9)	(76.6, 94.5)	(77.5, 87.4)

Abbreviations: MCyR=major cytogenetic response, CCyR=complete cytogenetic response

[a]Cytogenetic response results are presented for the respective evaluable populations (imatinib-resistant n=182; imatinib-intolerant n=80; Total n = 262). [b]Exploratory cohort

[c]These are cumulative rates of response representing minimum follow up of 60 months

Unconfirmed response definition: a response which may or may not be confirmed at least 28 days later

Cytogenetic response criteria: Major Cytogenetic response included Complete (0% Ph+ metaphases) or partial (1%-35%) cytogenetic responses. Cytogenetic responses were based on the percentage of Ph-positive metaphases among ≥20 metaphase cells in each bone marrow sample. Fluorescent in situ hybridization analysis (≥200 cells) could be used for post-baseline cytogenetic assessments if ≥20 metaphases were not available.

[d] Including patients (N) who received at least one dose of bosutinib

The Kaplan-Meier estimate of retaining MCyR at Month 60 was 71.1% (95% CI: [62.6%, 78.0%]). By Year 5, the median duration of MCyR was not reached. The median time to MCyR was 12.3 weeks (95% CI: 12.1, 12.7) for all evaluable responders (n=262) who were previously treated with imatinib only.

Of the 284 patients in the CP CML population that were previously treated with imatinib, 15 patients [5.3% (95% CI: 3.0, 8.6)] had confirmed disease transformation to AP or BP while on treatment with BOSULIF.

CP CML previously treated with imatinib and another TKI

A total of 119 patients with CP CML who were imatinib-resistant or intolerant and received at least 1 additional prior TKI therapy (ie. dasatinib and/or nilotinib) were enrolled and treated. Patients had a median age of 56 years (range 20 to 79 years), most were <65 years of age (77%), and slightly less than half (45%) of patients were male. Most patients were white (73%) or Asian (13%). Patients had an ECOG performance score of 0 (71%) or 1 (28%) at baseline (data was missing for 1 patient). Slightly more than half of patients (55%) had received prior interferon

therapy and 8% had undergone a stem cell transplant. The most common reasons for stopping imatinib treatment were disease progression (70%) and intolerance (30%).

Among the 119 patients receiving BOSULIF, all patients received prior therapy with imatinib (resistant or intolerant), 38 patients were dasatinib-resistant, 50 were dasatinib-intolerant, and 26 were nilotinib resistant, and 1 patient was nilotinib intolerant. There were 4 patients who received BOSULIF following all previous TKI treatments: 1 was resistant to all 3 prior TKI therapies (imatinib, dasatinib,nilotinib), 1 was intolerant of all 3 prior TKI therapies, 1 was resistant to imatinib and nilotinib and intolerant to dasatinib, and 1 was intolerant to imatinib and nilotinib and resistant to dasatinib. Of these 119 patients, 112 were evaluable for efficacy.

The efficacy results of these 119 patients are summarized in Table 17.

Table 17. Efficacy Results in Ph+ CP CML Patients Previously Treated with Imatinib and Dasatinib and/or Nilotinib

	IM + (NI + D) or IM + NI Intolerant[b] (n=5)	**IM + D Resistant[b] (n=38)**	**IM + D Intolerant[b] (n=50)**	**IM + NI Resistant[b] (n=26)**	**Total (N=119)**
By Week 24					
MCyR (95% CI)[a]	40.0% (5.3,85.3)	30.6% (16.4,48.1)	20.0% (9.6,34.6)	26.9% (11.6,47.8)	25.9% (18.1,35.0)
CCyR (95% CI)[a]	20.0% (0.5,71.6)	8.3% (1.8,22.5)	17.8% (8.0,32.1)	11.5% (2.5,30.2)	13.4% (7.7,21.1)
Cumulative[c]					
MCyR (95% CI)[a]	40.0% (5.3,85.3)	38.9% (23.1,56.5)	42.2% (27.7,57.9)	38.5% (20.2,59.4)	40.2% (31.0,49.9)
CCyR (95% CI)[a]	40.0% (5.3,85.3)	22.2% (10.1,39.2)	40.0% (25.7,55.7)	30.8% (14.3,51.8)	32.1% (23.6,41.6)
Progression free survival[d]					
KM at year 4, (95% CI)	53.3% (6.8, 86.3)	65.0% (42.1, 80.7)	73.7% (54.7, 85.7)	55.6% (30.6, 74,7)	65.1% (53.1, 74.8)
Overall survival[d]					
KM at year 4, (95% CI)	80% (20.4, 96.9)	66.1% (44.5, 80.9)	79.3% (63.1, 89.0)	86.5% (62.9, 95.6)	77.0% (66.9, 84.4)

Abbreviations: CI=confidence interval, D=dasatinib, IM=imatinib, NA=not applicable, NI=nilotinib, MCyR=major cytogenetic response, CCyR = complete cytogenetic response

[a.] Cytogenetic response results are presented for the respective evaluable populations (IM + (NI + D) or IM + NI Intolerant n=5; IM + D resistant n=36; IM + D intolerant n=46; IM + NI resistant n=26; Total n=112).

[b]Exploratory cohort

[c]These are cumulative rates of response representing minimum follow up of 48 months

Unconfirmed response definition: a response which may or may not be confirmed at least 28 days later

[d] Including patients (N) who received at least one dose of bosutinib

The K-M estimate of retaining MCyR at Month 48 (Week 192) was 69.3% (95% CI: [52.3%, 81.3%]) for CP CML patients previously treated with imatinib and another TKI. The median duration was not reached. The median time to MCyR was 12.3 weeks (95% CI: 12.0, 14.1) for all evaluable responders that were previously treated with imatinib and another TKI.

Of the 119 patients in the CP CML population that were previously treated with imatinib and another TKI, 5 patients [4.2% (95% CI: 1.4, 9.5)] had confirmed disease transformation to AP while on treatment with BOSULIF; no patients transformed to BP.

Advanced Phase CML

A total of 143 advanced phase leukemia patients were treated with BOSULIF, including 79 patients with AP CML and 64 with BP CML. In the AP CML cohort, the median age was 51.0 years (range 18.0 to 83.0 years), 90% were <65 years of age, and a little more than half (56%) of patients were male. Most patients were white (58%) or Asian (28%). Most patients had an ECOG performance score of 0 (57%) or 1 (41%) at baseline. Half of patients (52%) had received prior interferon therapy, 32% had received prior dasatinib therapy, 19% had received prior nilotinib therapy, and 9% had a prior stem cell transplant. The primary reasons for stopping imatinib were disease progression (86%) and AE (14%). Of the 79 AP CML patients, 72 patients were evaluable for efficacy.

In the BP CML cohort, the median age was 47.0 years (range 19.0 to 82.0 years), 84% were <65 years of age, and a little more than half (66%) of patients were male. Most patients were white (58%) or Asian (23%). Patients had an ECOG performance score of 0 (34%), 1 (45%), or 2 (20%) at baseline. Thirty-one percent (31%) had received prior interferon therapy, 34% had received prior dasatinib therapy, 17% had received prior nilotinib therapy, and 6% had a prior stem cell transplant. The primary reasons for stopping imatinib were disease progression (84%) and AE (16%). Of the 64 BP CML patients, 60 patients were evaluable for hematologic response and 52 patients were evaluable for cytogenetic response.

The efficacy results in the advanced leukemia patients are summarized in Table 18.

Table 18. Efficacy Results in Accelerated Phase and Blast Phase Patients Treated with at Least Imatinib

	AP IM Only[b] (n=49)	AP Multi TKI[b] (n= 30)	AP Total (N=79)	BP IM Only[b] (n= 36)	BP Multi TKI[b] (n= 28)	BP Total (N= 64)
OHR						
Cumulative by Week 48 (95% CI)[a]	67.4% (51.5,80.9)	41.4% (23.5,61.1)	56.9% (44.7,68.6)	38.2% (22.2,56.4)	15.4% (4.4,34.9)	28.3% (17.5,41.4)
Cumulative[c]						
MCyR (95% CI)[a]	47.8% (32.9,63.1)	26.9%) (11.6,47.8)	40.3% (28.9,52.5)	50.0% (31.3,68.7)	20.8% (7.1,42.2)	37.0% (24.3,51.3)
CCyR[c] (95% CI)[a]	34.8% (21.4,50.3)	23.1% (9.0,43.7)	30.6% (20.2,42.5)	36.7% (19.9,56.1)	16.7% (4.7,37.4)	27.8% (16.5,41.6)
Progression Free Survival[d]						
K-M at year 4 (95% CI)	38.0% (21.7, 54.1)	46.4% (19.5, 69.7)	40.8% (26.6, 54.5)	8.1% (0.7, 28.1)	7.6% (0.7, 26.4)	8.0% (1.7, 21.2)
Overall Survival[d]						
K-M at year 4 (95% CI)	65.7% (48.6, 78.3)	45.1% (25.4, 63.0)	58.4% (45.6, 69.1)	20.7% (2.0, 53.2)	16.7% (5.6, 32.9)	20.1% (6.2, 39.8)

Abbreviations: OHR=overall hematologic response

[a]Hematologic and cytogenetic response results are presented for the evaluable population (AP IM Only/AP Multi TKI/AP Total n=43/29/72 for hematologic and n=46/26/72 for cytogenetic; BP IM Only/BP Multi TKI/BP Total n=34/26/60 for hematologic and n=30/24/54 for cytogenetic).
[b]Exploratory cohort
[c]These are cumulative rates of response representing minimum follow up of 48 months
Confirmed hematologic response definition: two consecutive responses at least 28 days apart.
Unconfirmed cytogenetic response definition: a response which may or may not be confirmed at least 28 days later
[d] Including patients (N) who received at least one dose of bosutinib

Overall hematologic response (OHR) = major hematologic response (complete hematologic response + no evidence of leukemia) or return to chronic phase (RCP). All responses were confirmed after 4 weeks. Complete hematologic response (CHR) for AP and BP CML: WBC ≤ institutional ULN, 100,000/mm^3 ≤ platelets <450,000/mm^3, absolute neutrophil count (ANC) ≥1.0 x 10^9 /L, no blasts or promyelocytes in peripheral blood, <5% myelocytes + metamyelocytes in bone marrow, <20% basophils in peripheral blood, and no extramedullary involvement. No evidence of leukemia (NEL): Meets all other criteria for CHR except may have thrombocytopenia (20,000/mm^3 < platelets <100,000/mm^3) and/or neutropenia (0.5 x 10^9 /L < ANC < 1.0 x 10^9 /L. Return to chronic phase (RCP)=disappearance of features defining accelerated or blast phases but still in chronic phase

In AP CML subjects, 56.9% of subjects maintained or attained confirmed OHR. The K-M estimate of maintaining OHR at Month 48 (week 192) was 52.0% (95% CI: [32.3%, 68.5%]). The median duration of OHR was not reached as of the minimum 48 month follow-up.

For the 40.3% of patients with MCyR, the median duration of MCyR was 84.0 weeks (95% CI: [24.0, not estimable]). The median time to MCyR was 12.0 weeks (95% CI: 11.9, 12.1) for all evaluable responders.

Of the 79 patients in the AP CML population, 3 patients [3.8% (95% CI: 0.8, 10.7)] had confirmed disease transformation to BP while on treatment with BOSULIF.

In BP CML subjects, 28.3% maintained or attained confirmed OHR. The median duration of OHR was 32.0 weeks (95% CI: [29.0, 54.6]).

For the 37.0% of patients with MCyR, the median duration of MCyR was 29.1 weeks (95% CI: [11.9, 38.3]). The median time to MCyR was 8.2 weeks (95% CI: 4.3, 12.0) for all evaluable responders.

DETAILED PHARMACOLOGY

Nonclinical Pharmacodynamics

Nonclinical studies indicate that bosutinib is a potent inhibitor of the kinase activity of BCR-ABL, the oncogenic driver of CML, and SRC kinases, which contribute to BCR-ABL signalling. Several other kinases and kinase families are inhibited by bosutinib, including STE20, EPH, TEC and AXL family kinases. Bosutinib did not inhibit PDGF receptor or c-KIT and is not a substrate for multidrug resistance transporters. Modeling studies indicate that bosutinib binds to the catalytic domain of BCR-ABL.

Bosutinib (10 μM) has affinity towards several off-target proteins including non-selective adrenergic Alpha 1 and Alpha 2 receptors, histamine H2 receptor, non-selective central muscarinic receptor, serotonin transporter receptor, Sigma non-selective receptor, sodium site 2 ion channel and neurokinin A receptor.

In vitro, bosutinib inhibits BCR-ABL signaling in CML cells. Proliferation of established CML cell lines as well as patient-derived CML progenitor cells is inhibited by bosutinib treatment. Bosutinib overcomes imatinib-resistance acquired via mutations in BCR-ABL and by BCR-ABL independent mechanisms such as overexpression of the Src family kinase LYN. Murine myeloid cells that require BCR-ABL activity to grow were inhibited by bosutinib treatment. When mutated forms of BCR-ABL resistant to imatinib were expressed in place of wild type BCR-ABL, sixteen of eighteen of these imatinib-resistant mutants of BCR-ABL were inhibited by bosutinib, with the T315I mutation as one notable exception. Oral administration of bosutinib shrinks BCR-ABL-dependent tumors growing in nude mice, and can inhibit growth of tumors dependent on expression of imatinib-resistant forms of BCR-ABL.

Nonclinical Pharmacokinetics

Bosutinib pharmacokinetics were characterized by moderate to high CL and high Vss in mice, rats, and dogs after single-dose IV administration. Absorption was moderate to rapid in all evaluated species. A higher drug plasma concentration was observed in female rats compared to males. Bosutinib was widely distributed in various rat tissues, as measured by the presence of radioactivity, but did not cross the blood brain barrier. In Caco-2 cell monolayers, bosutinib was a substrate of the efflux transporters P-gp, BCRP, and MRPs. Moreover, oral absorption and bioavailability did not appear to be limited by these efflux transporters. The pharmacokinetic and toxicokinetic results showed that sufficient drug exposure was achieved with the oral route of administration for pharmacology and toxicology evaluations.

After oral administration to rats, [^{14}C]bosutinib-derived radioactivity was well distributed to most tissues and organs, with the exception of the brain, and was consistent with a high volume of distribution for bosutinib. The uptake and retention of [^{14}C]bosutinib-derived radioactivity was particularly prominent in the pigmented tissues such as those containing melanin. In gravid Sprague-Dawley (S-D) rats, drug-derived radioactivity was associated with the placenta, amniotic fluid and fetuses. In lactating S-D rats, drug-derived radioactivity was excreted into milk and detected in plasma from nursing pups.
Bosutinib and its *N*-desmethyl metabolite (M5) showed high, concentration-independent protein binding in mouse, rat, rabbit, dog, and human plasma.

Bosutinib was the predominant component in plasma of mice, rats, dogs, and humans following oral administration of unlabeled or [^{14}C] bosutinib. In humans, the prominent circulating metabolites were oxydechlorinated bosutinib (M2) and M5. In rats, systemic exposure to M2 (administered as the metabolite) and to M5 (at the no observed adverse effect level (NOAEL), in the 6-month toxicity study) were approximately 2- to 3-fold and 2-fold higher, respectively, than that observed in humans after oral administration of a single 500 mg dose of bosutinib. Based on the exposure comparisons, coverage for M2 and M5 was achieved in the nonclinical toxicology species. The M5, M2 and M6 metabolites demonstrated only 5% inhibitory activity compared to bosutinib itself in *in vitro* cellular assays.

In vitro, bosutinib was predominantly metabolized by CYP3A4. *In vitro*, bosutinib inhibited CYP3A4/5 (non-mechanism-based inhibition) and CYP2C19 and CYP2D6 activity at

concentrations that were 26- to 71-fold higher than the C_{max} in humans at 500 mg once daily. Bosutinib also reduced mRNA expression of CYP3A4 and CYP1A2.

After oral administration of [^{14}C]bosutinib to rats, dogs, and humans, the major route of excretion of radioactivity was via the feces.

TOXICOLOGY

Bosutinib has been evaluated in safety pharmacology, repeated dose toxicity, genotoxicity, reproductive toxicity, and phototoxicity studies. No safety pharmacology studies were conducted to specifically assess the secondary pharmacological effects of bosutinib on the gastrointestinal or renal systems. Toxicology studies indicated that effects on the gastrointestinal system were likely.

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 at exposures approximately > 8-fold and > 24-fold, respectively, those in CML patients receiving the 500 mg dose and > 11-fold those in CML patients receiving the 400 mg dose (comparing C_{max} and based on unbound fraction in the respective species). Bosutinib activity *in vitro* in hERG assays suggested a potential for prolongation of cardiac ventricular repolarization (QT interval). 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 interval of the electrocardiogram (ECG) at exposures up to 3-fold the human exposure resulting from the clinical dose of 400 mg and 2-fold the human exposure resulting from the clinical dose of 500 mg (comparing C_{max} and based on unbound fraction 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 interval (<10 msec) were observed at exposures ranging from approximately 5.8- to 20-fold the human exposure resulting from the clinical dose of 400 mg and 4.2- to 14.6-fold the human exposure resulting from the clinical exposure following the 500 mg dose. The relationship between the observed effects and drug treatment was inconclusive.

In a echocardiography study in male Sprague-Dawley rats, increased left ventricular (LV) diastolic thickness, decreased LV endocardial area and decreased mitral valve deceleration time were observed at week 4 in animals treated with daily 50 mg/kg bosutinib. Bosutinib exposure was approximately 1.2-fold the human AUC following administration of the 500 mg daily dose. These effects were not observed at subsequent time points (6 and 8 weeks) despite higher exposures (1.5-fold the human AUC at the 500 mg dose in the same animals at the 8 week time point). No apparent heart weight increase or change in left ventricular function was reported. The toxicological implications of these findings are not understood. In a subsequent echocardiography study of similar design, male and female Sprague-Dawley rats received bosutinib treatment (50 mg/kg/day) for 6 months. Bosutinib-treated female rats had slightly increased absolute (9%) and statistically significant increased relative heart weight (13%) when compared to vehicle-treated animals at biopsy. Increased end diastolic volume, diastolic posterior wall thickness, LV endocardial and epicardial areas and LV mass were observed in bosutinib-treated female rats starting at 2 months and persisting until 6 months, which is

consistent with LV hypertrophy. No significant LV deficit (examined by fractional shortening or ejection fraction) was observed. No heart weight increase or LV mass increase based on echocardiography was found in bosutinib-treated male animals. Bosutinib exposure in male and female rats was approximately 0.8- and 4.4-fold clinical exposure following the 500 mg daily dose, respectively.

Following a single oral (10 mg/kg) administration of [14C] radiolabeled bosutinib to lactating Sprague-Dawley rats; radioactivity was readily excreted into breast milk as early as 0.5 h 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

The carcinogenic potential of bosutinib was evaluated in the 2-year rat carcinogenicity study. The systemic exposures (AUCs) of unbound bosutinib in male and female rats at the highest doses tested (25 and 15 mg/kg/day) were approximately 1.8 (males) and 3.8-times (females) the human exposure resulting from the clinical dose of 400 mg and 1.4 (males) and 2.8-times (females) the human exposure resulting from the clinical dose of 500 mg. Bosutinib was not carcinogenic.

Developmental Toxicity

In a rabbit developmental-toxicity study at a maternally-toxic dosage, there were fetal anomalies observed (fused sternebrae, and two fetuses had various visceral observations), and a slight decrease in fetal body weight. The exposure at the highest dose tested in rabbits (10 mg/kg) that did not result in adverse fetal effects was 0.9-times the human exposure resulting from the clinical dose of 400 mg and 0.7-times that in humans at the 500 mg dose (based on unbound AUC in the respective species) of bosutinib. When administered to pregnant rats on GD 19, bosutinib was highly distributed to the placenta and crossed to fetal tissues. Bosutinib was also excreted via mammary milk and was detected in the plasma of lactating rat pups.

In a rat pre- and postnatal development study, there were reduced number of pups born at ≥30 mg/kg/day, decreased postnatal survival (including increased incidence of total litter loss) and decreased growth of offspring after birth occurred at 70 mg/kg/day. The dose at which no adverse development effects were observed in offspring was a maternal dose of 10 mg/kg/day, which resulted in exposures equal to 1.3 and 1.0 times human exposure resulting from the clinical dose of 400 mg and 500 mg, respectively (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 evidence for a mutagenic potential of bosutinib. Bosutinib was evaluated for its potential to induce micronucleated polychromatic erythrocytes (PCEs) in the bone marrow of male CD-1 mice at single oral (gavage) doses of 0 (vehicle control), 500, 1000, or 2000 mg/kg. There was no bosutinib related, statistically significant increase, compared with controls, in the frequency of micronucleated PCEs in the

bone marrow of male mice at bosutinib doses up to 2000 mg/kg. Therefore, bosutinib did not induce cytogenetic damage in this study at exposures as high as 47-fold the clinical exposure following the 500 mg dose.

Impairment of Fertility

There was no evidence of adverse developmental toxicity in rats treated with bosutinib less than 10 mg/kg/day at exposures equal to 1.6-times the human exposure resulting from the clinical dose of 400 mg and 1.2-times the human exposure at the 500 mg dose (based on unbound AUC in the respective species) of bosutinib.

Based on non-clinical findings, bosutinib has the potential to impair reproductive function and fertility in humans. In a rat fertility study, fertility was slightly decreased in males at 70 mg/kg/day when mated with treatment-naive females. Females mated with treatment-naive males were observed with decreased body weight gain and food consumption, increased embryonic resorptions at ≥10 mg/kg/day (40% of human exposure), decreases in implantations, and viable embryos at 30 mg/kg/day (1.4 times the human exposure). 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 and 0.3-times, respectively, the human exposure resulting from the clinical dose of 400 mg, and 0.4 and 0.2-times, respectively, the human exposure resulting from the clinical dose of 500 mg (based on unbound AUC in the respective species).

Maternal toxicity was associated with bosutinib, when given throughout gestational days 6 to 15 to pregnant rabbits, and occurred at all doses (10, 30 and 60 mg/kg/day). With regard to fetal toxicity, bosutinib exposure during gestation caused early embryonic death at 60 mg/kg/day and decreased fetal weights at 30 and 60 mg/kg/day. Bosutinib did not cause any major malformations in fetuses. Together, the data indicate that bosutinib administration during pregnancy leads to maternal toxicity and at higher doses fetal toxicity (early fetal death).

Phototoxicity

Bosutinib was shown 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.

Repeated-dose Toxicity

Repeated-dose toxicity studies in rats of up to 6 months in duration and in dogs of 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 fecal changes and were associated with decreased food consumption, and body weight loss which occasionally led to deaths or elective euthanasia. The exposure comparisons indicate that exposures that did not elicit adverse effects 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). In the 2-year rat carcinogenicity study, adverse gastrointestinal effects,

(mucosal collagen deposition) were at dose levels as low as 1.5 mg/kg and exposures as low as 0.08-fold those in humans at the 500 mg daily dose. There was an increased incidence and/or severity of focal/multifocal lobular atrophy of the exocrine pancreas which was accompanied by varying degrees of chronic inflammatory cell infiltrate and fibrosis at exposures in male and female rats 0.23-fold and 2.8-fold, respectively, the human exposure at 500 mg. The pancreatic effects were accompanied by acinar apoptosis in male rats at an exposure 1.4-fold the human exposure at the 500 mg dose level. Renal tubular atrophy was observed at an increased incidence, but not severity, in male and female rats at exposures 1.4- and 2.8-fold respectively, the exposure at the daily 500 mg dose. In the highest dose group, there were more early deaths and euthanasia of undetermined causes in male rats at 1.4-fold (25 mg/kg/day) the human exposure, but not in female rats at 2.8-fold (15 mg/kg/day) the human exposure at the 500 mg dose level.

PART III: CONSUMER INFORMATION

Pr BOSULIF®
(bosutinib tablets)

This leaflet is part III of a three-part "Product Monograph" published when BOSULIF was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about BOSULIF. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
BOSULIF is used to treat adults:

- who have a new diagnosis of a white blood cell cancer called Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in a chronic phase or
- who have Ph+ CML in a chronic, accelerated, or blast phase (the blood cancer grows faster in accelerated or blast than in chronic phase) and for whom previous medicines to treat Ph+ CML have either not worked or not been suitable.

A qualified healthcare professional experienced in the used of anticancer therapies and in the treatment of CML should prescribe BOSULIF.

BOSULIF has not been studied in children.

What it does:
BOSULIF works by slowing down the growth and spread of cancer cells in patients with CML.

When it should not be used:
Do not use BOSULIF if you:

- are allergic to BOSULIF or any of the other ingredients of BOSULIF
- have an abnormal electrical signal of the heart (prolongation of QT interval)
- have uncorrectable low levels of potassium or magnesium
- have liver failure

What the medicinal ingredient is:
bosutinib

What the nonmedicinal ingredients are:
croscarmellose sodium, iron oxide yellow (for 100 mg tablet), iron oxide yellow and iron oxide red (for 400 mg tablet[§]), iron oxide red (for 500 mg tablet), magnesium stearate, microcrystalline cellulose, poloxamer, polyethylene glycol, polyvinyl alcohol, povidone, talc, and titanium dioxide

[§] Not commercially available in Canada

What dosage forms it comes in:
Tablets 100 mg, 400 mg[§], and 500 mg

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Serious side effects with BOSULIF include:

- Drug interactions with inhibitors or inducers of CYP3A4 enzyme. Do NOT use BOSULIF with strong and moderate CYP3A4 inhibitors and inducers (see Serious Drug and Drug-Food Interactions below)
- Gastrointestinal problems (vomiting and diarrhea)
- Liver problems
- Heart problems that may lead to death
- Fluid in the lungs and around the heart (fluid retention)
- Bleeding
- Abnormal electrical signal of the heart

BEFORE you use BOSULIF talk to your doctor or pharmacist if you:

- have or have had in the past, a liver, heart, pancreas or kidney problem.
- are pregnant, or plan to become pregnant as BOSULIF could harm an unborn baby. Discuss contraception with your doctor if there is any possibility that you may become pregnant. BOSULIF must not be used during pregnancy.
- are breastfeeding or planning to breast-feed. Do not breast-feed during treatment with BOSULIF as it could harm your baby.
- have gastrointestinal problems (vomiting and diarrhea).
- have ever had or might now have a hepatitis B virus infection (a viral infection of the liver). This is because during treatment with BOSULIF, hepatitis B may become active again which can be fatal in some cases. Your doctor will test for signs of this infection before treatment with BOSULIF and while on treatment if required.

BOSULIF may cause harm to your unborn child. Both male and female patients must use an effective birth control method such as a condom while taking BOSULIF, during interruptions of treatment and for at least 4 weeks after the last dose. This must be done even if you have undergone a successful vasectomy. If you or your partner become pregnant, tell your doctor right away.

Male and female fertility may be affected by treatment with BOSULIF.

Do not drive or operate machinery if you feel tired or dizzy, or experience any change in vision while taking BOSULIF.

INTERACTIONS WITH THIS MEDICATION

Serious Drug and Drug-Food Interactions

Do not take any products or juice containing grapefruit, star fruit, pomegranate, Seville oranges or similar fruits while taking BOSULIF. They may change the amount of BOSULIF in your body.

While taking BOSULIF, avoid taking drugs that:

- Are used to treat fungal infections such as ketoconazole, itraconazole, voriconazole, posaconazole, and fluconazole
- Are used to treat human immunodeficiency virus (HIV) infections such as lopinavir/ritonavir, atazanavir, indinavir, nelfinavir, saquinavir, darunavir/ritonavir, amprenavir, efavirenz, etravirine and fosamprenavir.
- Are used to treat high blood pressure such as dialtiazem, verapamil, bosentan and mibefradil
- Are used to treat depression such as nefazodone and St. John's wort (a herbal preparation obtained without a prescription)
- Are used to treat bacterial infections such as erythromycin, clarithromycin, ciprofloxacin and nafcillin
- Are used to treat tuberculosis such as rifampicin
- Are used to treat epilepsy such as phenytoin and carbamazepine
- Are used to prevent and control nausea (feeling sick) and vomiting, such as aprepitant
- Are used to treat certain types of sleep disorders, such as modafinil
- Are used to treat cancers , such as crizotinib and imatinib
- Are used to treat hepatitis C virus, such as telaprevir
- Are used to treat low sodium, such as conivaptan

Tell your doctor about the medicines you take, including prescription medicines, non-prescription medicines, vitamins, and herbal supplements. BOSULIF and certain other medicines can interact with each other and cause serious side effects. Drugs that may interact with BOSULIF include:

- Other cancer medicine such as vandetanib, sunitinib, nilotinib, lapatinib.
- Quinidine, amiodarone and other medicines for heart rhythm problems (anti-arrhythmic drugs).
- Lansoprazole, dexlansoprazole, omeprazole, esomeprazole, pantoprazole, rabeprazole (medicines for reducing stomach acid).
- Amitryptiline and imipramine (medicine for depression).
- Pimozide, ziprasidone, haloperidol (medicine for psychoses).
- Quinine and chloroquine (medicine to treat malaria).
- Domperidone, dolasetron and ondansetron (medicine for nausea and vomiting).
- Formoterol and salmeterol (asthma drugs).
- Water pills, laxatives (medicine that decrease electrolyte levels).

Know the medicines you take. Keep a list of your medicines, both prescription and non-prescription, and show it to your doctor and pharmacist when you get a new medicine. Do not take other medicines with BOSULIF until you have talked with your doctor.

PROPER USE OF THIS MEDICATION

BOSULIF should be taken with a meal. Swallow BOSULIF tablets whole . Do not cut, crush or dissolve the tablets.
Do not drink grapefruit juice or eat grapefruit, grapefruit products, star fruit, pomegranate, Seville oranges and other similar fruits. They may change the amount of BOSULIF in your body.

Always take BOSULIF exactly as your doctor has told you.

You should check with your doctor or pharmacist if you are not sure.

Usual Adult Dose (≥18 years of age):
Patients with newly-diagnosed chronic phase Ph+ CML:
400 mg once daily.
Patients with chronic, accelerated, or blast phase Ph+ CML whose previous medicines to treat Ph+CML have either not worked or not been suitable: 500 mg once daily.
Your doctor may adjust the dose.

Overdose:
If you think you have taken too much BOSULIF contact your healthcare professional , hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

If possible, show the doctor the pack, or this leaflet. You may require medical attention.

Missed Dose:
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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

BOSULIF may cause serious side effects, such as:

Liver problems - Your doctor may do blood tests to check your liver function during treatment with BOSULIF:

- your skin or the whites of your eyes turn yellow
- your urine turns dark or brown (tea color)

Hepatitis B virus reactivation – A previous hepatitis B viral infection (an infection of the liver) to become active again when you have had a hepatitis B infection in the past (hepatitis B reactivation), which can be fatal in some cases.

Kidney problems – Your doctor may do blood and/or urine tests to check your kidney function before and during treatment with BOSULIF

Gastrointestinal problems:

- you have abdominal pain, nausea, diarrhea, or vomiting
- you have blood in your vomit or have black, bloody or tarry stools

Low blood cell counts:

- you have signs of infection such as fever, or severe chills
- you have unexpected bleeding or bruising without having an injury

Your body may hold too much fluid (fluid retention):

- you have difficulty breathing, chest pain, or a cough
- you have swelling in your hands, ankles, or feet

Heart problems:

- dizziness, palpitations or if you faint

Tell your doctor right away if you develop or have developed any of the above serious side effects.

Tell your doctor if you have any side effect that bothers you or that does not go away.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very common	Reduction in the number of platelets, red blood cells, white blood cells, and neutrophils (type of white blood cells)		√	
	Diarrhea, vomiting, stomach pain, nausea, decrease of appetite	√		
	Fatigue and headache	√		
	Shortness of breath		√	
	Changes in blood test to determine if BOSULIF is affecting your liver, kidney, and/or pancreas		√	
	Sore throat combined with runny nose (nasopharyngitis)	√		
	Skin rash which may be itchy and/or generalized	√		
	Feeling of instability (dizziness)		√	
	Joint pain	√		
Common	Increased blood pressure		√	
	Fever associated with a marked decrease in the number of neutrophils (a type of white blood cells)		√	
	Fluid accumulation in the sac-like covering of the heart		√	
	Stomach irritation (gastritis)		√	
	Fever	√		
	Swelling of hands, feet or face		√	
	Weakness, chest pain, pain		√	
	Kidney failure, kidney impairment		√	
	Influenza, bronchitis	√		
	Toxic damage to the liver, abnormal hepatic function including liver disorder		√	
	Infection of the lung (pneumonia)		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
		Only if severe	**In all cases**	
	High level of potassium in the blood, low level of phosphorous in the blood, excessive loss of body fluid (dehydration)		√	
	Back pain, pain in the muscle	√		
	Alteration of the sense of taste (dysgeusia)	√		
	Fluid on the lungs (pleural effusion)		√	
	Itching, urticaria (hives), acne	√		
Uncommon	Inflammation of the sac-like covering of the heart (pericarditis)		√	
	Blood in stools and throwing up blood		√	
	Defect in cardiac rhythm that predisposes to syncope, dizziness and palpitation		√	
	Respiratory failure		√	
	Allergic reaction, potentially life-threatening (anaphylactic shock)		√	
	Abnormally high blood pressure in the arteries of the lungs (pulmonary hypertension)		√	
	Severe skin disorder due to an allergic reaction (erythema multiforme), exfoliative (scaly, peeling) rash, skin eruption		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
		Only if severe	**In all cases**	
Rare	Fever, sore mouth/throat, cough, and muscle aches may occur followed by development of severe red rash that blisters/peels with mouth sores and painful, red, watery eyes.			√

This is not a complete list of side effects. For any unexpected effects while taking BOSULIF, contact your doctor or pharmacist.

HOW TO STORE IT

Store at 20°C to 25°C.

Keep BOSULIF and all other medicines, out of the reach and sight of children.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about BOSULIF:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp); the manufacturer's website www.pfizer.ca, or by calling 1-800-463-6001.

This leaflet was prepared by Pfizer Canada ULC
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