PRODUCT MONOGRAPH

# Pr BOSULIF™

bosutinib

Tablets, 100 mg and 500 mg

Protein-tyrosine kinase inhibitor

**BOSULIF (bosutinib tablets), 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, and for whom subsequent treatment with imatinib, nilotinib and dasatinib is not clinically appropriate,**

**has been issued marketing authorization with conditions, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the authorization.**

™ Wyeth LLC,
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Kirkland, Quebec
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Date of Revision:
29 July 2015



Submission Control No: 183372

**This product has been approved under the Notice of Compliance with Conditions (NOC/c) policy for one or all of its indicated uses.**

**What is a Notice of Compliance with Conditions (NOC/c)?**

An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products approved under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

**What will be different about this Product Monograph?**

The following Product Monograph will contain boxed text at the beginning of each major section clearly stating the nature of the market authorization. Sections for which NOC/c status holds particular significance will be identified in the left margin by the symbol NOC/c. These sections may include, but are not limited to, the following:

- Indications and Clinical Uses;
- Action;
- Warnings and Precautions;
- Adverse Reactions;
- Dosage and Administration; and
- Clinical Trials.

**Adverse Drug Reaction Reporting and Re-Issuance of the Product Monograph**

Health care providers are encouraged to report Adverse Drug Reactions associated with normal use of these and all drug products to Health Canada's Health Product Safety Information Division at 1-866-234-2345. The Product Monograph will be re-issued in the event of serious safety concerns previously unidentified or at such time as the sponsor provides the additional data in support of the product's clinical benefit. Once the latter has occurred, and in accordance with the NOC/c policy, the conditions associated with market authorization will be removed.

## Table of Contents

# PRBOSULIF™

bosutinib tablets

## PART I: HEALTH PROFESSIONAL INFORMATION

BOSULIF (bosutinib tablets), indicated for,

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has been issued marketing authorization with conditions, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the authorization.

## SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | Clinically Relevant Nonmedicinal Ingredients |
|---|---|---|
| Oral | Tablets 100 mg and 500 mg | Coating: iron oxide yellow, iron oxide red.<br>Tablet:<br>*For a complete listing see Dosage Forms, Composition and Packaging section.* |

NOC/c

## INDICATIONS AND CLINICAL USE

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, and for whom subsequent treatment with imatinib, nilotinib and dasatinib is not clinically appropriate.

Market authorization with conditions is based on cytogenetic and hematologic response rates observed in a single-arm, Phase 1/ 2 study. Overall survival benefit has not been demonstrated.

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.

## NOC/c 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. 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).

## NOC/c WARNINGS AND PRECAUTIONS

**Serious Warnings and Precautions**

- Drug interactions with inhibitors or inducers of CYP3A4. The concomitant use of BOSULIF with potent 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 potent 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 potent 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. Six (1.1%) 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 of newly diagnosed Ph+ CP CML patients, 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 10.2% of patients in the Phase 1/ 2 study, with Grade 3 or 4 cardiac-related events reported in 3.5% of patients. Atrial fibrillation (2.1%) (Grade 3 or 4 in 0.9%), cardiac failure congestive (1.8%), and tachycardia (1.8%) were most commonly reported. Grade 3 or 4 events of acute myocardial infarction, cardiac failure, and coronary artery disease were reported in 0.5% of patients each, as well as coronary artery stenosis (0.4%), left ventricular dysfunction (0.4%), and pulmonary edema (0.2%). In the Phase 3 study, 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 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 18 patients (3.2%). Sixteen patients had a Grade 3 or 4 effusion (13 patients had Grade 3 or 4 pleural effusions [2.3%] and 3 patients [0.5%] had a Grade 3 or 4 pericardial effusion). In the Phase 3 study, 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, the median time of onset for diarrhea (all grades) was 2 days and the median duration per event was 2 days. Eighty-one percent (81%) of patients treated with BOSULIF experienced diarrhea, with 8.1% Grade 3/4.

In newly diagnosed CML CP patients, 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. 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 9.6% of patients. Hemorrhage events included duodenal ulcer hemorrhage, eye hemorrhage, gastrointestinal hemorrhage, operative hemorrhage, pericardial hemorrhage, rectal hemorrhage, retroperitoneal hemorrhage, subarachnoid hemorrhage, vaginal hemorrhage, and cerebral hemorrhage.

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 (ALT, AST).

In the 570 patients from the safety population, 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 18 days.

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 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 (3%) and amylase and Grade 3 or 4 acute pancreatitis 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

## 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 Grade 3 or 4 cellulitis in 0.5% of subjects in the Phase 1 /2 study. BOSULIF may predispose patients who are immunocompromised or older patients to bacterial, fungal, viral or protozoan infections.

## 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%) (see ADVERSE REACTIONS).

**Hypersensitivity**

Cases of Grade 3 or 4 hypersensitivity, anaphylactic shock leading to hospitalization, and urticaria have been reported with BOSULIF. 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). 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. 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. 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, 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.

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. A total of 29 subjects (5%) in the study had a total of 35 adverse events (AEs) of renal failure/impairment (including renal failure acute, renal failure, renal failure chronic and renal impairment). 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. 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 respiratory disorders including dyspnoea, pleural effusion, respiratory failure, acute pulmonary edema, pulmonary hypertension, pneumonitis, and interstitial lung disease.

**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)*:** No clinically relevant age-related pharmacokinetic differences have been observed in the elderly. No specific dose recommendation is necessary in the elderly.

***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).

***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).

NOC/c

## ADVERSE REACTIONS

### Adverse Drug Reaction Overview

The safety information provided in this section represents an assessment of the adverse reactions from 1119 patients who received at least 1 oral dose of single-agent BOSULIF in Ph+ CML, other Ph+ leukemias, and advanced malignant solid tumors.

### 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.*

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

The single-arm Phase 1/2 clinical study enrolled a total of 571 patients with Ph+ chronic, accelerated, or blast phase chronic myelogenous leukemia (CML) or Ph+ acute lymphoblastic leukemia (ALL) who were resistant or intolerant to prior therapy. The safety population (received at least 1 dose of BOSULIF) included 570 patients. Within the safety population, the 288 patients with Ph+ CP CML who were resistant or intolerant to imatinib had a median duration of BOSULIF treatment of 22 months, and a median dose intensity of 484 mg/day. There were 118 patients with Ph+ CP CML who were resistant or intolerant to ≥ 2 tyrosine kinase inhibitors (TKIs), including imatinib, dasatinib, and/or nilotinib. These patients had a median duration of BOSULIF treatment of 8 months; and a median dose intensity of 478 mg/day. There were 164 patients with Ph+ AP CML, BP CML, or ALL who were resistant or intolerant to at least imatinib. These patients had a median duration of BOSULIF treatment of 10 months, 3 months, and 1 month, respectively. The median dose intensities were 483 mg/day, 500 mg/day, and 500 mg/day in the AP CML, BP CML, and Ph+ ALL cohorts, respectively.

Adverse reactions of any toxicity grade reported for ≥20% of patients in the Phase 1/2 safety population were diarrhea (79.5% of which 7.7% were Grade 3/4), nausea (41.6% of which 1.1% were Grade 3/4), vomiting (34.4% of which 2.5% were Grade 3/4), abdominal pain (28.9% of which 0.7% were Grade 3/4), thrombocytopenia (35.1% of which 23.9% were Grade 3/4), and rash (27.9% of which 6.3% were Grade 3/4). Table 1 below presents adverse reactions of any toxicity and grades 3/4 very commonly reported (frequencies ≥10%) in the Phase 1/2 safety population.

**Table 1:**
**Number (%) of CML and Ph+ALL 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* Imatinib Resistant or Intolerant N=288 | | CP* Resistant or Intolerant ≥2 TKIs N=118 | | AP* CML, BP* CML, Ph+ ALL Resistant or Intolerant to at least Imatinib N=164 | |
|---|---|---|---|---|---|---|
| **System Organ Class Preferred Term** | **All Grades n (%)** | **Grade 3/4 n (%)** | **All Grades n (%)** | **Grade 3/4 n (%)** | **All Grades n (%)** | **Grade 3/4 n (%)** |
| **Any Adverse Reactions** | 283 (98.3) | 154 (53.5) | 118 (100) | 60 (50.8) | 154 (93.9) | 85 (51.8) |
| **Blood and lymphatic system disorders** | | | | | | |
| Thrombocytopenia | 113 (39.2) | 69 (24.0) | 43 (36.4) | 29 (24.6) | 44 (26.8) | 38 (23.2) |
| Anemia | 47 (16.3) | 21 (7.3) | 17 (14.4) | 3 (2.5) | 30 (18.3) | 14 (8.5) |
| Neutropenia | 41 (14.2) | 23 (8.0) | 20 (16.9) | 16 (13.6) | 28 (17.1) | 26 (15.9) |
| Leukopenia | 30 (10.4) | 13 (4.5) | 3 (2.5) | 0 | 15 (9.1) | 10 (6.1) |
| **Nervous system disorders** | | | | | | |
| Headache | 22 (7.6) | 0 | 16 (13.6) | 1 (0.8) | 10 (6.1) | 0 |
| **Gastrointestinal disorders** | | | | | | |
| Diarrhea | 240 (83.3) | 26 (9.0) | 96 (81.4) | 10 (8.5) | 117 (71.3) | 8 (4.9) |
| Nausea | 119 (41.3) | 4 (1.4) | 51 (43.2) | 0 | 67 (40.9) | 2 (1.2) |
| Vomiting | 94 (32.6) | 8 (2.8) | 38 (32.2) | 1 (0.8) | 64 (39.0) | 5 (3.0) |
| Abdominal pain | 101 (35.1) | 2 (0.7) | 32 (27.1) | 0 | 32 (19.5) | 2 (1.2) |
| **Skin and subcutaneous tissue disorders** | | | | | | |
| Rash | 89 (30.9) | 25 (8.7) | 26 (22.0) | 5 (4.2) | 44 (26.8) | 6 (3.7) |
| Pruritus | 18 (6.3) | 2 (0.7) | 12 (10.2) | 1 (0.8) | 5 (3.0) | 0 |
| **General disorders and administration site-conditions** | | | | | | |
| Fatigue | 44 (15.3) | 3 (1.0) | 22 (18.6) | 1 (0.8) | 16 (9.8) | 3 (1.8) |
| **Investigations** | | | | | | |
| Alanine-aminotransferase increased | 60 (20.8) | 21 (7.3) | 14 (11.9) | 7 (5.9) | 14 (8.5) | 7 (4.3) |
| Aspartate-aminotransferase increased | 51 (17.7) | 11 (3.8) | 7 (5.9) | 2 (1.7) | 11 (6.7) | 3 (1.8) |

* CP = Chronic Phase; AP = Accelerated Phase; BP = Blast Phase
Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
NOTE: Cluster terms used in the analysis are defined below.
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
Fatigue includes the following preferred terms: Fatigue, Malaise

**Table 1:**
**Number (%) of CML and Ph+ALL 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* Imatinib Resistant or Intolerant N=288 | | CP* Resistant or Intolerant ≥2 TKIs N=118 | | AP* CML, BP* CML, Ph+ ALL Resistant or Intolerant to at least Imatinib N=164 | |
|---|---|---|---|---|---|---|
| **System Organ Class Preferred Term** | **All Grades n (%)** | **Grade 3/4 n (%)** | **All Grades n (%)** | **Grade 3/4 n (%)** | **All Grades n (%)** | **Grade 3/4 n (%)** |

Leukopenia includes the following preferred terms: Leukopenia, White blood cell count decreased
Neutropenia includes the following preferred terms: Neutropenia, Neutrophil count decreased
Rash includes the following preferred terms: Rash, Rash generalised, Rash macular, Rash maculo-papular, Rash papular, Rash pruritic
Thrombocytopenia includes the following preferred terms: Platelet count decreased, Thrombocytopenia

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

**Table 2:**
**Number (%) of CML and Ph+ALL 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* Imatinib Resistant or Intolerant N=288 | | CP* Resistant or Intolerant ≥2 TKIs N=118 | | AP* CML, BP* CML, Ph+ ALL Resistant or Intolerant to at least Imatinib N=164 | |
|---|---|---|---|---|---|---|
| **System Organ Class Preferred Term** | **All Grades n (%)** | **Grade 3/4 n (%)** | **All Grades n (%)** | **Grade 3/4 n (%)** | **All Grades n (%)** | **Grade 3/4 n (%)** |
| **Infections and infestations** | | | | | | |
| Pneumonia | 1 (0.3 ) | 1 (0.3 ) | 0 | 0 | 7 (4.3 ) | 3 (1.8 ) |
| Respiratory tract infection | 1 (0.3 ) | 0 | 2 (1.7 ) | 0 | 2 (1.2 ) | 0 |
| Influenza | 2 (0.7 ) | 0 | 2 (1.7 ) | 0 | 0 | 0 |
| **Blood and lymphatic system disorders** | | | | | | |
| Febrile Neutropenia | 0 | 0 | 1 (0.8) | 1 (0.8) | 2 (1.2) | 1 (0.6) |
| **Immune system disorders** | | | | | | |
| Drug hypersensitivity | 3 (1.0) | 2 (0.7) | 4 (3.4) | 1 (0.8) | 1 (0.6) | 0 |
| **Metabolism and nutrition disorders** | | | | | | |
| Decreased appetite | 28 (9.7) | 1 (0.3) | 11 (9.3) | 1 (0.8) | 10 (6.1) | 0 |
| Hypophosphataemia | 7 (2.4) | 3 (1.0) | 3 (2.5) | 0 | 3 (1.8) | 2 (1.2) |
| Dehydration | 2 (0.7) | 0 | 1 (0.8) | 0 | 3 (1.8) | 1 (0.6) |
| Hyperkalaemia | 2 (0.7) | 1 (0.3) | 3 (2.5) | 0 | 1 (0.6) | 0 |
| **Nervous system disorders** | | | | | | |
| Dizziness | 13 (4.5) | 0 | 6 (5.1) | 0 | 6 (3.7) | 0 |
| Dysgeusia | 5 (1.7) | 0 | 2 (1.7) | 0 | 2 (1.2) | 0 |
| **Cardiac disorders** | | | | | | |
| Pericardial effusion | 2 (0.7) | 1 (0.3) | 3 (2.5) | 1 (0.8) | 4 (2.4) | 1 (0.6) |
| **Respiratory, thoracic and mediastinal disorders** | | | | | | |
| Pleural effusion | 8 (2.8) | 1 (0.3) | 9 (7.6) | 1 (0.8) | 9 (5.5) | 5 (3.0) |

**Table 2:**
**Number (%) of CML and Ph+ALL 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* Imatinib Resistant or Intolerant N=288 | | CP* Resistant or Intolerant ≥2 TKIs N=118 | | AP* CML, BP* CML, Ph+ ALL Resistant or Intolerant to at least Imatinib N=164 | |
|---|---|---|---|---|---|---|
| **System Organ Class Preferred Term** | **All Grades n (%)** | **Grade 3/4 n (%)** | **All Grades n (%)** | **Grade 3/4 n (%)** | **All Grades n (%)** | **Grade 3/4 n (%)** |
| Dyspnoea | 13 (4.5) | 1 (0.3) | 6 (5.1) | 1 (0.8) | 4 (2.4) | 1 (0.6) |
| Cough | 7 (2.4) | 0 | 1 (0.8) | 0 | 2 (1.2) | 0 |
| Respiratory failure | 0 | 0 | 0 | 0 | 2 (1.2) | 1 (0.6) |
| **Gastrointestinal disorders** | | | | | | |
| Gastritis | 4 (1.4) | 0 | 1 (0.8) | 0 | 4 (2.4) | 1 (0.6) |
| **Hepatobiliary disorders** | | | | | | |
| Hepatic function abnormal | 9 (3.1 ) | 5 (1.7 ) | 2 (1.7 ) | 2 (1.7 ) | 1 (0.6 ) | 0 |
| Hepatotoxicity | 2 (0.7 ) | 0 | 2 (1.7 ) | 2 (1.7 ) | 1 (0.6 ) | 0 |
| **Skin and subcutaneous tissue disorders** | | | | | | |
| Acne | 6 (2.1) | 0 | 1 (0.8) | 0 | 2 (1.2) | 0 |
| Urticaria | 5 (1.7) | 0 | 3 (2.5) | 1 (0.8) | 1 (0.6) | 1 (0.6) |
| Exfoliative rash | 3 (1.0) | 0 | 0 | 0 | 1 (0.6) | 0 |
| **Musculoskeletal and connective tissue disorders** | | | | | | |
| Arthralgia | 13 (4.5) | 0 | 7 (5.9) | 0 | 6 (3.7) | 0 |
| Myalgia | 9 (3.1) | 0 | 5 (4.2) | 1 (0.8) | 7 (4.3) | 2 (1.2) |
| Back pain | 3 (1.0) | 0 | 2 (1.7) | 0 | 1 (0.6) | 0 |
| **Renal and urinary disorders** | | | | | | |
| Renal failure | 0 | 0 | 1 (0.8) | 0 | 2 (1.2) | 0 |
| **General disorders and administration site conditions** | | | | | | |
| Asthenia | 23 (8.0 ) | 4 (1.4 ) | 4 (3.4 ) | 0 | 10 (6.1 ) | 0 |
| Pyrexia | 19 (6.6 ) | 1 (0.3 ) | 4 (3.4 ) | 0 | 9 (5.5 ) | 2 (1.2 ) |

**Table 2:**
**Number (%) of CML and Ph+ALL 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* Imatinib Resistant or Intolerant N=288 | | CP* Resistant or Intolerant ≥2 TKIs N=118 | | AP* CML, BP* CML, Ph+ ALL Resistant or Intolerant to at least Imatinib N=164 | |
|---|---|---|---|---|---|---|
| **System Organ Class Preferred Term** | **All Grades n (%)** | **Grade 3/4 n (%)** | **All Grades n (%)** | **Grade 3/4 n (%)** | **All Grades n (%)** | **Grade 3/4 n (%)** |
| Edema | 16 (5.6 ) | 1 (0.3 ) | 9 (7.6 ) | 0 | 6 (3.7 ) | 0 |
| Pain | 7 (2.4 ) | 0 | 2 (1.7 ) | 0 | 1 (0.6 ) | 0 |
| Chest pain | 5 (1.7 ) | 0 | 1 (0.8 ) | 0 | 3 (1.8 ) | 0 |
| **Investigations** | | | | | | |
| Lipase increased | 15 (5.2) | 10 (3.5) | 7 (5.9) | 4 (3.4) | 2 (1.2) | 1 (0.6) |
| Blood creatinine increased | 5 (1.7) | 0 | 7 (5.9) | 0 | 4 (2.4) | 0 |
| Blood bilirubin increased | 7 (2.4) | 0 | 2 (1.7) | 1 (0.8) | 3 (1.8) | 2 (1.2) |
| Blood amylase increased | 7 (2.4) | 3 (1.0) | 4 (3.4) | 0 | 2 (1.2) | 1 (0.6) |
| Blood creatine phosphokinase increased | 7 (2.4) | 3 (1.0) | 1 (0.8) | 0 | 0 | 0 |
| Gamma-glutamyltransferase increased | 5 (1.7) | 1 (0.3) | 2 (1.7) | 1 (0.8) | 0 | 0 |

* CP = Chronic Phase; AP = Accelerated Phase; BP = Blast Phase
Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
Blood bilirubin increased includes the following preferred terms: Blood bilirubin increased, Hyperbilirubinaemia
Chest pain includes the following preferred terms: Chest discomfort, Chest pain
Edema includes the following preferred terms: Face oedema, Localised oedema, Oedema, Oedema peripheral
Electrocardiogram QT prolonged includes the following preferred terms: Electrocardiogram QT prolonged, Long QT syndrome
Hepatic function abnormal includes the following preferred terms: Hepatic function abnormal, Liver disorder
Hepatotoxicity includes the following preferred terms: Hepatitis toxic, Hepatotoxicity
Lipase increased includes the following preferred terms: Hyperlipasaemia, Lipase increased
Pneumonia includes the following preferred terms: Bronchopneumonia, Pneumonia, Pneumonia primary atypical
Rash includes the following preferred terms: Rash, Rash generalised, Rash macular, Rash maculo-papular, Rash papular, Rash pruritic
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. Six (1.1%) 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.

**Tabulated Summary of Adverse Reactions**

The following adverse reactions in Table 3 were reported in patients in pooled clinical studies with BOSULIF. They represent an evaluation of the adverse reaction data from 1119 patients who received at least 1 dose of single-agent BOSULIF in Ph+ CML, 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 3:**
**Adverse Reactions for BOSULIF**
**Pooled Safety**
**(Ph+ CML, other Ph+ leukemias, and advanced malignant solid tumors)**
**N=1119**

| | |
|---|---|
| **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) |
| Common | pneumonia (including bronchopneumonia, primary atypical pneumonia), influenza, bronchitis, nasopharyngitis |
| **Blood and lymphatic system disorders** | |
| Very common | thrombocytopenia, anemia, neutropenia |
| Common | leucopenia |
| Uncommon | febrile neutropenia, granulocytopenia |
| **Immune system disorders** | |
| Common | drug hypersensitivity |
| Uncommon | anaphylactic shock |
| **Metabolism and nutrition disorders** | |
| Very common | decreased appetite |
| Common | hyperkalemia, hypophosphatemia, dehydration |
| **Nervous system disorders** | |
| Very common | headache |
| Common | dizziness, dysgeusia |
| **Ear and labyrinth disorders** | |
| Common | tinnitus |
| **Cardiac disorders** | |
| Common | pericardial effusion |
| Uncommon | pericarditis |
| **Respiratory, thoracic and mediastinal disorders** | |
| Very common | dyspnea |
| Common | pleural effusion |
| Uncommon | acute pulmonary edema, respiratory failure, pulmonary hypertension |
| **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 gastric hemorrhage, upper gastrointestinal hemorrhage) |

**Table 3:**
**Adverse Reactions for BOSULIF**
**Pooled Safety**
**(Ph+ CML, other Ph+ leukemias, and advanced malignant solid tumors)**
**N=1119**

| | |
|---|---|
| Uncommon | acute pancreatitis |
| **Hepatobiliary disorders** | |
| Common | hepatotoxicity (including toxic hepatitis, cytolytic hepatitis), abnormal hepatic function (including liver disorder) |
| Uncommon | liver injury |
| **Skin and subcutaneous tissue disorders** | |
| Very common | rash (including maculopapular rash, pruritic rash, generalized rash, papular rash) |
| Common | urticaria, pruritus, acne |
| Uncommon | erythema multiforme, exfoliative rash, drug eruption |
| **Musculoskeletal and connective tissue disorders** | |
| Very common | arthralgia |
| Common | back pain, myalgia |
| **Renal and urinary disorders** | |
| Common | acute renal failure, renal failure |
| Uncommon | renal impairment |
| **General disorders and administration site conditions** | |
| Very common | fatigue (including malaise), pyrexia, edema (including face edema, localized edema, peripheral edema) |
| Common | asthenia, chest pain (including chest discomfort), pain |
| **Investigations** | |
| Very common | increased alanine aminotransferase, increased aspartate aminotransferase |
| Common | increased lipase, increased blood amylase, increased gamma-glutamyltransferase, increased blood creatine phosphokinase, increased blood bilirubin, electrocardiogram QT prolonged, 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 4 below.

**Table 4:**
**Adverse Events for BOSULIF**
**Pooled Safety**
**(Ph+ CML, other Ph+ leukemias, and advanced malignant solid tumors)**
**N=1119**

| | |
|---|---|
| **Infections and infestations** | C. difficile colitis, Hepatitis A, pneumonia fungal, respiratory tract infection fungal, bacteremia, enterococcal sepsis, orchitis, pseudomonal sepsis, septic shock |
| **Neoplasms benign and malignant (including cysts and polyps)** | basal cell carcinoma, gastric cancer, keratoacanthoma, non-small lung cancer, squamous cell carcinoma, bladder cancer, malignant melanoma, metastatic neoplasm, rectal cancer recurrent |
| **Metabolism and nutrition disorders** | hypogammglobulinaemia, hyperuricemia, hyperlipasemia, hypermagnesemia, hypokalemia, decreased appetite, hyponatremia, diabetes mellitus, hypocalcemia, tumour lysis syndrome |
| **Psychiatric disorders** | dissociative disorder, depression, confusional state, mental status changes |
| **Nervous system disorders** | cerebral hemorrhage, subarachnoid hemorrhage, hemicephalalgia, syncope, grand mal convulsion, somnolence, encephalopathy, encephalitis post varicella |
| **Cardiac disorders** | arterial occlusive disease, angina pectoris, atrial fibrillation, cardiac failure congestive, left ventricular dysfunction, palpitations, arrhythmia, bradycardia, cardiac tamponade, coronary artery disease, coronary artery stenosis, dilatation atrial, Long QT syndrome, myocardial infarction, supraventricular extrasystoles |
| **Vascular disorders** | hypertension, vasculitis, aortic stenosis, carotid arteriosclerosis, deep vein thrombosis |
| **Respiratory, thoracic and mediastinal disorders** | interstitial lung disease, pneumonitis, lung infiltration , acute respiratory failure, pulmonary fibrosis, pulmonary embolism |
| **Gastrointestinal disorders** | diarrhea hemorrhagic, duodenal ulcer hemorrhage, sigmoiditis, melaena, rectal hemorrhage, retroperitoneal hemorrhage |
| **Hepatobiliary disorders** | hyperbilirubinemia , cholangitis acute, cholelithiasis, cholecystitis |
| **Skin and subcutaneous tissue disorders** | erythematous, angioedema, photosensitivity reaction, alopecia, leukocytoclastic vasculitis, circumoral edema |
| **Musculoskeletal and connective tissue** | fractures ( including cervical, vertebral, clavicle, facial bones, foot, hand, humerus, rib, tooth, upper limb), spinal column stenosis |

**Table 4:**
**Adverse Events for BOSULIF**
**Pooled Safety**
**(Ph+ CML, other Ph+ leukemias, and advanced malignant solid tumors)**
**N=1119**

| | |
|---|---|
| **disorders** | |
| **Renal and urinary disorders** | calculus bladder, tubulointerstitial nephritis, glomerulonephritis chronic, cystitis hemorrhagic, nephrolithiasis |
| **Reproductive system disorders** | vaginal hemorrhage, breast hyperplasia, cervical dysplasia, vaginal dysplasia |
| **General disorders and administration site conditions** | serositis |
| **Investigations** | increased total bilirubin, increased blood bilirubin (conjugated), increased blood bilirubin (unconjugated), platelet count decreased, blood lactate dehydrogenase increased, blood phosphorus decreased, pancreatic enzymes increased, weight increased |
| **Hemorrhage (multiple SOCs)** | subdural hemorrhage, cerebral hemorrhage, cerebral infarction, duodenal ulcer hemorrhage, eye hemorrhage, gastrointestinal hemorrhage, operative hemorrhage, pericardial hemorrhage, rectal hemorrhage, retroperitoneal hemorrhage, subarachnoid hemorrhage, vaginal hemorrhage, cerebral hemorrhage |

SOCs: System Organ Classes based on MedDRA (Medical Dictionary for Regulatory Activities)

**ECG Findings**

In the Phase 3 study of newly diagnosed Ph+ CP CML patients, 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.

**Abnormal Hematologic and Clinical Chemistry Findings**

Table 5 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 5:**
**Number (%) 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=288 n (%) | CP* CML Resistant or Intolerant ≥2 TKIs N=118 n (%) | AP* CML, BP* CML, Ph+ ALL Resistant or Intolerant to at least Imatinib N=164 n (%) |
|---|---|---|---|
| **Hematology parameters** | | | |
| Platelet Count <50 X $10^9$/L | 70 (24.3%) | 30 (25.4%) | 98 (59.8%) |
| Absolute Neutrophil Count <1 X $10^9$/L | 49 (17%) | 23 (19.5%) | 64 (39%) |
| Hemoglobin (Low) <80 g/L | 39 (13.5%) | 10 (8.5%) | 56 (34.1%) |
| **Biochemistry parameters** | | | |
| SGPT/ALT >5.0 X ULN | 30 (10.4%) | 8 (6.8%) | 8 (4.9%) |
| SGOT/AST >5.0 X ULN | 13 (4.5%) | 4 (3.4%) | 4 (2.4%) |
| Lipase >2 X ULN | 24 (8.3%) | 8 (6.8%) | 5 (3%) |
| Phosphorus (Low) <0.6 mmol/L | 25 (8.7%) | 3 (2.5%) | 13 (7.9%) |
| Total Bilirubin (High) >3xULN | 0 | 3 (2.5%) | 3 (1.8%) |

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

Table 6 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 6: 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) |

## DRUG INTERACTIONS

**Serious Drug and Drug-Food Interactions**

- Potent and moderate CYP3A inhibitors increase BOSULIF exposure. Avoid concomitant use of these inhibitors.
- Potent 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 potent CYP3A inhibitors (e.g., including but not limited to ritonavir, indinavir, nelfinavir, saquinavir, ketoconazole, itraconazole, voriconazole, posaconazole, troleandomycin, clarithromycin, telithromycin, mibefradil, nefazodone, conivaptan), or moderate CYP3A inhibitors (e.g., including but not limited to fluconazole, darunavir, erythromycin, diltiazem, dronedarone, atazanavir, aprepitant, amprenavir, imatinib, verapamil, grapefruit products including star fruit, pomegranate, Seville oranges and other similar fruits that are known to inhibit CYP3A4, tofisopam ciprofloxacin, cimetidine) 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 potent 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 substrates may occur.

**Drugs That May Decrease Bosutinib Plasma Concentrations**

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

Based on the large reduction in bosutinib exposure that occurred when BOSULIF was co-administered with rifampin (potent CYP3A inducer), increasing the dose of BOSULIF when co-administering with potent 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 P-glycoprotein (P-gp):** Caution should be used if BOSULIF is administered with drugs that are substrates of P-glycoprotein (P-gp). An *in vitro* study suggests that BOSULIF has the potential to increase the plasma concentrations of drugs that are P-gp substrates, such as digoxin.

**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.

**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 potent CYP3A4 inducer. Avoid the concomitant use of potent 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-Lifestyle 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.

## NOC/c DOSAGE AND ADMINISTRATION

**Recommended Dose and Dosage Adjustment**

The recommended dose and schedule of BOSULIF is 500 mg orally once daily, swallowed whole, with a meal. 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 the Phase 1/2 clinical trial, treatment with BOSULIF continued until disease progression or until it was no longer tolerated by the patient.

In the Phase 1/2 clinical trial, dose escalation to 600 mg once daily with food was allowed only in patients who failed to reach complete hematological response (CHR) by week 8 or a complete cytogenetic response (CCyR) by week 12, at the recommended starting dosage, and who did not have Grade 3 or higher adverse reactions. Dose escalations are expected to result in greater toxicity.

**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 400 mg 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 400 mg once daily once the toxicity has resolved. If clinically appropriate, re-escalation of the dose to 500 mg once daily may be considered.

**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 7).

**Table 7: Dose Adjustments for Neutropenia and Thrombocytopenia**

| | |
|---|---|
| ANC[a] <1.0x10$^9$/L<br><br>and/or<br><br>Platelets <50x10$^9$/L | Hold BOSULIF until ANC ≥1.0x10$^9$/L and platelets ≥50x10$^9$/L.<br><br>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.<br><br>If either of these cytopenias recurs, reduce dose by 100 mg upon recovery and resume treatment.<br><br>Doses less than 300 mg/day have not been evaluated. |

[a]Absolute Neutrophil Count

**Dosing Considerations**

**Concomitant Use With CYP3A Inhibitors**
Avoid the concomitant use of potent 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 potent 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 potent 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**
In patients with moderate renal impairment [creatinine clearance (CrCL) 30 to 50 mL/min, estimated by the Cockroft-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 Cockroft-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, the patient should not take an additional dose 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.*

## NOC/c 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 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 8. 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:** Absolute bioavailability of BOSULIF has not been established. Following administration of a single oral dose of BOSULIF (500 mg) with food in healthy subjects, absorption was relatively slow, with a median time-to-peak concentration ($t_{max}$) reached after 6 hours. The mean standard deviation (SD) $C_{max}$ value was 112 (29) ng/mL, and the mean (SD) AUC was 2740 (790) ng•h/mL. Food increased bosutinib $C_{max}$ 1.8-fold and bosutinib AUC 1.7-fold compared to the fasting state. After 15 consecutive daily doses of BOSULIF (500 mg) with food in patients with CML, the mean (SD) $C_{max}$ value was 200 (12) ng/mL, and the mean (SD) AUC was 3650 (425) ng•h/mL.

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

**Distribution:** After administration of a single dose of BOSULIF (500 mg) with food to healthy subjects, bosutinib had a mean apparent volume of distribution (standard deviation) of 7,700 L (±2,940 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 healthy subjects given a single-oral dose of BOSULIF (500 mg) with food, the mean (SD) terminal phase elimination half-life ($t_{1/2}$) was 33.8 (7.7) hours, and the mean (SD) clearance (Cl/F) was 197 (57) 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 25°C; excursions permitted to 15- 30°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:*
Microcrystalline cellulose, croscarmellose sodium, poloxamer, povidone, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide yellow.

*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:*
Microcrystalline cellulose, croscarmellose sodium, poloxamer, povidone, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide red.

BOSULIF (bosutinib) tablets are available in the following packaging configurations (Table 9):

**Table 9: 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) | |
| 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

# PART II: SCIENTIFIC INFORMATION

BOSULIF (bosutinib tablets), 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, and for whom subsequent treatment with imatinib, nilotinib and dasatinib is not clinically appropriate,

has been issued marketing authorization with conditions, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the authorization.

## PHARMACEUTICAL INFORMATION

### Drug Substance

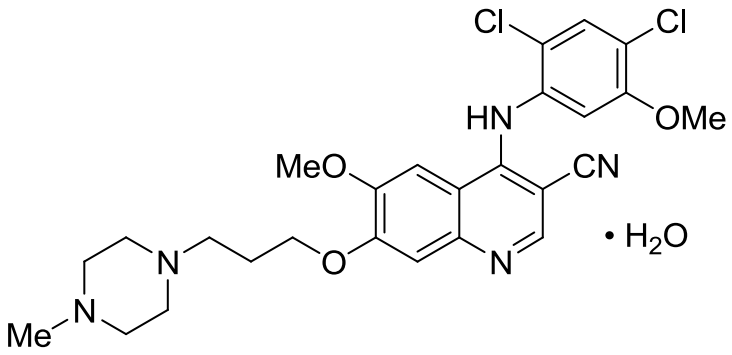
Proper name: Bosutinib

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: $C_{26}H_{29}Cl_2N_5O_3 \cdot H_20$ (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.

## NOC/c CLINICAL TRIALS

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

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 MCyR rate at week 24 in patients with imatinib-resistant CP CML who have had imatinib exposure only (primary endpoint analysis cohort). The efficacy endpoint used for the sample size calculation in CP CML was unconfirmed MCyR which included complete and partial cytogenetic responses. The efficacy endpoint used for the sample size calculation in both AP CML and BP CML was confirmed overall hematologic response (OHR), defined as either a major hematologic response (MHR) or return to chronic phase (RCP).

Secondary efficacy objectives were to estimate the MCyR rate in patients with imatinib-intolerant CP CML who have imatinib exposure only, estimate time to and duration of MCyR in patients with CP CML who have had imatinib exposure only, estimate the time to and duration of CHR, estimate the MCyR rate in patients with CP CML previously treated with imatinib who are also resistant to dasatinib or nilotinib or who are intolerant to dasatinib , estimate OS and PFS rates at 1 and 2 years, estimate the CHR rate in AP/BP CML patients treated with at least previous imatinib and estimate the OHR rate in AP/BP CML patients treated with at least previous imatinib. Table 10 presents the duration of follow-up and treatment with BOSULIF.

**Table 10. Duration of Follow-up and Treatment with BOSULIF**

| | CP CML | | AP CML | BP CML |
|---|---|---|---|---|
| | **Previously Treated with IM N=288** | **IM + (D or NI) N=118** | **N=76** | **N=64** |
| Minimum Time to Database Snapshot, months | 23.3 | 13.4 | 12.3 | 18.0 |
| Median Follow Up, months (range) | 31.8 (0.6-66.0) | 28.5 (0.3-56.2) | 26.5 (0.3-56.1) | 11.6 (0.4-48.0) |
| Median Duration of Treatment, months (range) | 22.1 (0.2-60.8) | 8.3 (0.2-51.8) | 10.1 (0.1-51.6) | 2.8 (0.03-44.2) |

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

Of these, 266 patients with CP CML treated with prior imatinib, 108 patients with CP CML treated with both imatinib and at least 1 additional TKI, and 129 patients with either AP CML or BP CML were evaluable for efficacy. Table 11 represents the demographic and baseline characteristics of the patients in the BOSULIF Phase 1/2 clinical study.

## Table 11. Demographic and Baseline Characteristics of Ph+ CP CML Patients Previously Treated

| Characteristic | Imatinib Resistant N=200 | Imatinib Intolerant N=88 | Total N=288 |
|---|---|---|---|
| Sex, n (%) | | | |
| Female | 84 (42) | 51 (58) | 135 (47) |
| Male | 116 (58) | 37 (42) | 153 (53) |
| Race, n (%) | | | |
| Asian | 43 (22) | 22 (25) | 65 (23) |
| Black | 12 (6) | 5 (6) | 17 (6) |
| Other[a] | 12 (6) | 7 (8) | 19 (7) |
| White | 133 (67) | 54 (61) | 187 (65) |
| Age category, n (%) | | | |
| Age <65 years | 163 (82) | 61 (69) | 224 (78) |
| Age ≥65 years | 37 (19) | 27 (31) | 64 (22) |
| ECOG Performance Status, n (%) | | | |
| 0 | 156 (78) | 64 (74) | 220 (77) |
| 1 | 44 (22) | 22 (25) | 66 (23) |
| 2 | 0 | 1 (1) | 1 |
| Missing | 0 | 1 | 1 |
| Number of prior therapies,[b] n (%) | | | |
| 1 | 128 (64) | 65 (74) | 193 (67) |
| 2 | 72 (36) | 23 (26) | 95 (33) |
| Prior interferon therapy, n (%) | | | |
| No | 128 (64) | 65 (74) | 193 (67) |
| Yes | 72 (36) | 23 (26) | 95 (33) |
| Prior imatinib therapy, n (%) | | | |
| Intolerant | 0 | 88 (100) | 88 (31) |
| Resistant | 200 (100) | 0 | 200 (69) |
| Prior stem cell transplant, n (%) | | | |
| No | 194 (97) | 86 (98) | 280 (97) |
| Yes | 6 (3) | 2 (2) | 8 (3) |
| Reason for stopping imatinib, n (%) | | | |
| Adverse event (intolerance) | 0 | 87 (99) | 87 (31) |
| Disease progression/Inadequate response | 186 (98) | 0 | 186 (67) |
| Other[c] | 0 | 1 (1) | 1 |
| Regimen completed | 3 (2) | 0 | 3 (1) |
| Missing[d] | 11 | 0 | 11 |

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.

***CP CML previously treated with imatinib only***

The efficacy results in the CP CML patients previously treated with imatinib are in Table 12. MCyR was achieved in 66 of 186 evaluable patients (35.5%; 95% CI: [28.6, 42.8]) at Week 24 in the primary endpoint analysis cohort (CP CML imatinib-resistant).

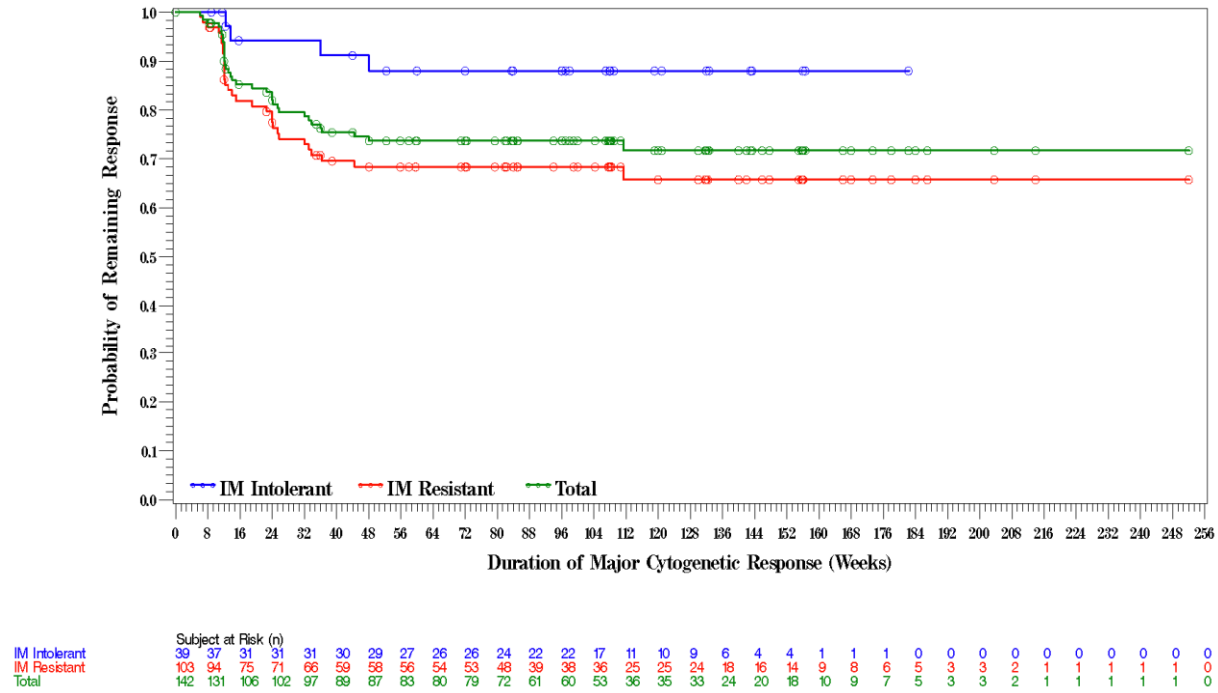
**Table 12:**
**Efficacy Results in Ph+ CP CML Patients Previously Treated with Imatinib Only**

| | Imatinib Resistant (n= 200) | Imatinib Intolerant[b] (n=88) | Total (N=288) |
|---|---|---|---|
| At Week 24 | | | |
| MCyR | 66/186 (35.5%) | 24/80 (30.0%) | 90/266 (33.8%) |
| (95% CI)[a] | (28.6,42.8) | (20.3,41.3) | (28.2,39.9) |
| CCyR | 45/186 (24.2%) | 20/80 (25.0%) | 65/266 (24.4%) |
| (95% CI)[a] | (18.2,31.0) | (16.0,35.9) | (19.4,30.1) |
| Cumulative | | | |
| MCyR (95% CI)[a] | 103/186 (55.4%) | 39/80 (48.8%) | 142/266 (53.4%) |
| (95% CI)[a] | (47.9,62.7) | (37.4,60.2) | (47.2,59.5) |
| CCyR (95% CI)[a] | 80/186 (43.0%) | 34/80 (42.5%) | 114/266 (42.9%) |
| (95% CI)[a] | (35.8,50.5) | (31.5,54.1) | (36.8,49.0) |

Abbreviations: MCyR=major cytogenetic response, CCyR=complete cytogenetic response
[a]Cytogenetic response results are presented for the respective evaluable populations (imatinib-resistant n=186; imatinib-intolerant n=80; Total n = 266). [b]Exploratory cohort
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.

The K-M plot for duration of MCyR in the CP CML patients previously treated with imatinib only is displayed in Figure 1. The median time to MCyR was 32.1 weeks (95% CI: 24.1, 48.0) for all evaluable patients that were previously treated with imatinib.

**Figure 1. Kaplan-Meir Estimate of the Duration of MCyR in Ph+ CP CML Patients Previously Treated with Imatinib Only**




Abbreviations: IM=imatinib, MCyR=major cytogenetic response

Of the 288 patients in the CP CML population that were previously treated with imatinib, 11 patients [3.8% (95% CI: 1.9, 6.7)] 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 118 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 (79%), and slightly less than half (45%) of patients were male. Most patients were white (72%) or Asian (14%). Patients had an ECOG performance score of 0 (74%) or 1 (26%) at baseline (data was missing for 1 patient). Slightly more than half of patients (52%) had received prior interferon therapy and 8% had undergone a stem cell transplant. The most common reasons for stopping imatinib treatment were disease progression (64%) and intolerance (31%).

Among the 118 patients receiving BOSULIF, all patients received prior therapy with imatinib (resistant or intolerant), 37 patients were dasatinib-resistant, 50 were dasatinib-intolerant, and 27 were nilotinib resistant; and 1 patient was nilotinib intolerant. There were 3 patients who received BOSULIF following all previous TKI treatments: 2 were resistant to all 3 prior TKI therapies (imatinib, dasatinib,nilotinib) and 1 was intolerant of all 3 prior TKI therapies.

The efficacy results of these 118 patients are summarized in Table 13.

**Table 13:**
**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=4) | IM + D Resistant[b] (n=37) | IM + D Intolerant[b] (n=50) | IM + NI Resistant[b] (n=27) | Total (N=118) |
|---|---|---|---|---|---|
| By Week 24 | | | | | |
| MCyR | 2/4(50.0%) | 9/35 (25.7%) | 11/43(25.6%) | 7/26(26.9%) | 29/108(26.9%) |
| (95% CI)[a] | (6.8,93.2) | (12.5,43.3) | (13.5,41.2) | (11.6,47.8) | (18.8,36.2) |
| CCyR | 1/4(25.0%) | 3/35 (8.6%) | 8/43 (18.6%) | 3/26(11.5%) | 15/108(13.9%) |
| (95% CI)[a] | (0.6,80.6) | (1.8,23.1) | (8.4,33.4) | (2.5,30.2) | (8.0,21.9) |

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=4; IM + D resistant n=35; IM + D intolerant n=43; IM + IM resistant n=26; Total n=108). [b]Exploratory cohort
Unconfirmed response definition: a response which may or may not be confirmed at least 28 days later

***Advanced Leukemia***

A total of 164 advanced phase leukemia patients were treated with BOSULIF, including 76 patients with AP CML and 64 with BP CML, and 24 with Ph+ ALL.

In the AP CML cohort, the median age was 50.5 years (range 18.0 to 83.0 years), 89% were <65 years of age, and a little more than half (55%) of patients were male. Most patients were white (61%) or Asian (26%). Most patients had an ECOG performance score of 0 (54%) or 1 (43%) at baseline. Half of patients (50%) had received prior interferon therapy, 33% had received prior dasatinib therapy, 20% 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 (12%).

In the BP CML cohort, the median age was 48.5 years (range 19.0 to 82.0 years), 83% were <65 years of age, and a little more than half (64%) of patients were male. Most patients were white (59%) or Asian (22%). Patients had an ECOG performance score of 0 (34%), 1 (44%), or 2 (22%) at baseline. Thirty percent (30%) had received prior interferon therapy, 36% had received prior dasatinib therapy, 19% had received prior nilotinib therapy, and 6% had a prior stem cell transplant. The primary reasons for stopping imatinib were disease progression (81%) and AE (19%).

In the Ph+ ALL cohort, the median age was 59.0 years (range 24.0 to 84 years), 54% were <65 years of age, and half (50%) were male. Most patients were white (79%). Patients had

an ECOG performance score of 0 (38%), 1 (46%), or 2 (17%) at baseline. Few patients (4%) had received prior interferon therapy, 33% had received prior dasatinib therapy, 1 patient had received prior nilotinib therapy, and 17% had a prior stem cell transplant. The reasons for stopping imatinib were disease progression (92%) and AE (8%).

The efficacy results in the advanced leukemia patients are summarized in Table 14.

**Table 14:**
**Efficacy Results in Accelerated-Phase and Blast Phase Patients Treated with at Least Imatinib**

| | AP IM Only[b] (n=45) | AP Multi TKI[b] (n=31) | AP Total (N=76) | BP IM Only[b] (n= 35) | BP Multi TKI[b] (n= 29) | BP Total (N= 64) |
|---|---|---|---|---|---|---|
| OHR | | | | | | |
| Cumulative by Week 48 (95% CI)[a] | 25/39 (64.1%) (47.2,78.8) | 13/30 (43.3%) (25.5,62.6) | 38/69 (55.1%) (42.6,67.1) | 12/33 (36.4%) (20.4,54.9) | 5/27 (18.5%) (6.3,38.1) | 17/60 (28.3%) (17.5,41.4) |

Abbreviations: OHR=overall hematologic response
[a]Hematologic response results are presented for the evaluable population (AP IM Only/AP Multi TKI/AP Total n=39/30/69; BP IM Only/BP Multi TKI/BP Total n=33/27/60). [b]Exploratory cohort
Confirmed response definition: two consecutive responses at least 28 days apart

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, 55.1% of subjects maintained or attained confirmed OHR. The median duration of OHR was not reached.

In BP CML subjects, 28.3% maintained or attained confirmed OHR. The median duration of OHR was 31.5 weeks (95% CI: [28.9, 48.0]).

## 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. *In vitro*, bosutinib inhibits P-gp and may have the potential to affect the absorption and/or pharmacokinetics of drugs that are substrates of P-gp, such as digoxin.

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 > 8-fold and > 24-fold, respectively, those in CML patients receiving the 500 mg dose. Bosutinib activity *in vitro* in hERG assays suggested a potential for prolongation of cardiac ventricular repolarization (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 2-fold (comparing $C_{max}$ and based on unbound fraction in the respective species) the clinical exposure at the 500 mg dose. A delayed increase in heart rate was observed. In an intravenous study in dogs, transient increases in heart rate and decreases in blood pressure and minimal prolongation of the QTc

interval (<10 msec) were observed at exposures ranging from 4.2- to 14.6-fold the clinical exposure following the 500 mg dose. The relationship between the observed effects and 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 1.4 and 2.8-times, respectively, the human exposure of unbound drug at the 500 mg dose. 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 0.7-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.

**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 1.2-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 0.4 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 exposure in humans after multiple dosing of 500 mg. 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.

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## PART III: CONSUMER INFORMATION

*BOSULIF (bosutinib tablets), 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, and for whom subsequent treatment with imatinib, nilotinib and dasatinib is not clinically appropriate,*

*has been issued marketing authorization with conditions, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the authorization.*

**What is a Notice of Compliance with Conditions (NOC/c)?**
An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products approved under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

**PrBOSULIF™**
**(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 (bosutinib) is used to treat a certain type of cancer called Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in adult patients for whom previous medicines have not worked and for whom subsequent treatment with the following medicines, imatinib, nilotinib and dasatinib, is not an option.

BOSULIF should be prescribed by a qualified healthcare professional who is experienced in the used of anticancer therapies and in the treatment of chronic myeloid leukemia.

BOSULIF has not been studied in children.

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

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

- are allergic (hypersensitive) to BOSULIF or any of the other ingredients of BOSULIF, listed under "**What the important nonmedicinal ingredients are:"**
- have an abnormal electrical signal of the heart (prolongation of QT interval)
- have uncorrectable low levels of potassium or magnesium
- have liver failure
- please refer to **Serious Side Effects, How Often they Happen and What to Do About Them**

**What the medicinal ingredient is:**
bosutinib

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

**What dosage forms it comes in:**
BOSULIF is available as oral tablets containing 100 mg or 500 mg of bosutinib.

BOSULIF 100 mg tablets are yellow film-coated with "Pfizer" on one side and "100" on the other side.

BOSULIF 500 mg tablets are red film-coated with "Pfizer" on one side and "500" on the other side.

## WARNINGS AND PRECAUTIONS

**Serious Warnings and Precautions**

Serious side effects with BOSULIF include:

- Drug interactions with inhibitors or inducers of CYP3A4. Concomitant use of BOSULIF with medicines belonging to a special group called potent and moderate CYP3A4 inhibitors should be avoided.
- 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 (QT prolongation)

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

- 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).

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 ritonavir, atazanavir, indinavir, nelfinavir, saquinavir, darunavir, amprenavir, efavirenz, and etravirine
- Are used to treat high blood pressure such as dialtizem, 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, and ciprofloxacin
- Are used to treat tuberculosis such as rifampicin, and rifabutin
- Are used to treat epilepsy such as phenytoin, carbamazepine, and phenobarbital
- Are used to treat irregular heart beat (anti-arrhythmic drugs) such as dronedarone
- Are used to prevent and control nausea (feeling sick) and vomiting, such as aprepitant
- Are used to treat a type of leukaemia, such as imatinib
- Are used in the treatment of heartburn and peptic ulcers due to too much acid in the stomach, such as cimetidine
- Are used to treat certain types of sleep disorders, such as modafinil

**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. Especially tell your doctor if you take:

- 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.
- Digoxin, used to treat irregular heart beat or heart failure.
- 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

**Usual Dose:**
The starting dose is 500 mg once daily. Your doctor may adjust the dose.

BOSULIF should be taken with a meal. Swallow BOSULIF tablets whole in water. 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.

**Overdose:**

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

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

**Missed Dose:**

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)

**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.

**The most common side effects of BOSULIF include:**

- Reduction in the number of platelets, red blood cells and/or neutrophils (type of white blood cells)
- Diarrhea, vomiting, stomach pain, nausea
- Fatigue, fever, swelling of hands, feet or face
- Respiratory tract infection
- Changes in liver blood test
- Decrease of appetite
- Joint pain
- Headache
- Shortness of breath
- Skin rash, which may be itchy and/or generalized

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 | |

**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 |
|---|---|---|---|---|
| **Very common** | Reduction in the number of platelets, red blood cells and neutrophils (type of white blood cells) | | √ | |
| | Diarrhea, vomiting, stomach pain, nausea | √ | | |
| | Fatigue | √ | | |
| | Changes in blood test to determine if BOSULIF is affecting your liver | | √ | |
| | Skin rash which may be itchy and/or generalized | √ | | |
| **Common** | Low white blood cells count (leucopenia) | | √ | |
| | Fever associated with a marked decrease in the number of neutrophils (a type of white blood cells) | | √ | |
| | Fluid accumulation in the sac-like covering the heart | | √ | |
| | Stomach irritation (gastritis) | | √ | |
| | Fever | √ | | |
| | Swelling of hands, feet or face | | √ | |
| | Decreased appetite | √ | | |
| | Joint pain | √ | | |
| | Headache | √ | | |
| | Shortness of breath | | √ | |

| 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** |
| | Weakness, chest pain, pain | | √ | |
| | Toxic damage to the liver, abnormal hepatic function including liver disorder | | √ | |
| | Infection of the lung (pneumonia) | | √ | |
| | Changes in blood tests to determine if BOSULIF is affecting your kidneys and.or pancreas. | | √ | |
| | 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 | √ | | |
| | Feeling of instability (dizziness) | | √ | |
| | Alteration of the sense of taste (dysgeusia) | √ | | |
| | Fluid on the lungs (pleural effusion) | | √ | |
| | Itching, urticaria (hives), acne | √ | | |
| Uncommon | Inflammation of the sac-like covering the heart (pericarditis) | | √ | |
| | Damage to liver | | √ | |
| | Influenza, bronchitis, nasopharyngitis | √ | | |
| | Loss of blood from the gastrointestinal tract | | √ | |

| 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** |
| | Defect in cardiac rhythm that predisposes to syncope, dizziness and palpitation | | √ | |
| | Kidney failure, kidney impairment | | √ | |
| | 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 | | √ | |

***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 25°C; excursions permitted to 15- 30°C.

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

**REPORTING SUSPECTED SIDE EFFECTS**

**You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:**

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**$ Report online at www.healthcanada.gc.ca/medeffect**
**$ Call toll-free at 1-866-234-2345**
**$ Complete a Canada Vigilance Reporting Form and:**
**- Fax toll-free to 1-866-678-6789, or**
**- Mail to: Canada Vigilance Program**
**Health Canada**
**Postal Locator 0701D**
**Ottawa, Ontario**
**K1A 0K9**

**Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.**

***NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.***

## MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: www.pfizer.ca or by contacting the sponsor, Pfizer Canada Inc., at: 1-800-463-6001 (Medical Information)

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