HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BOSULIF safely and effectively. See full prescribing information for BOSULIF

BOSULIF® (bosutinib) tablets, for oral use
Initial U.S. Approval: 2012

----------RECENT MAJOR CHANGES----------

Dosage and Administration, Renal Impairment (2.8) 4/2013

----------INDICATIONS AND USAGE----------

- BOSULIF is a kinase inhibitor indicated for the treatment of adult patients with chronic, accelerated, or blast phase Ph+ chronic myelogenous leukemia (CML) with resistance or intolerance to prior therapy. (1)

----------DOSAGE AND ADMINISTRATION----------

- Recommended Dose: 500 mg orally once daily with food. (2.1)
- Consider dose escalation to 600 mg daily in patients who do not reach complete hematologic response by week 8 or complete cytogenetic response by week 12 and do not have Grade 3 or greater adverse reactions. (2.2)
- Adjust dosage for hematologic and non-hematologic toxicity. (2.3, 2.4)
- Adjust dosage for hepatic and renal impairment. (2.7, 2.8)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 100 mg and 500 mg. (3)

----------CONTRAINDICATIONS----------

Hypersensitivity to BOSULIF. (4)

----------WARNINGS AND PRECAUTIONS----------

- Gastrointestinal toxicity: Monitor and manage as necessary. Withhold, dose reduce, or discontinue BOSULIF. (2.3, 5.1)
- Myelosuppression: Monitor blood counts and manage as necessary. (2.4, 5.2)
- Hepatic toxicity: Monitor liver enzymes at least monthly for the first three months and as needed. Withhold, dose reduce, or discontinue BOSULIF. (2.3, 5.3)
- Fluid retention: Monitor patients and manage using standard of care treatment. Withhold, dose reduce, or discontinue BOSULIF. (2.3, 5.4)
- Embryofetal toxicity: May cause fetal harm. Females of reproductive potential should avoid becoming pregnant while being treated with BOSULIF. (5.5)

----------ADVERSE REACTIONS----------

- Most common adverse reactions (incidence greater than 20%) are diarrhea, nausea, thrombocytopenia, vomiting, abdominal pain, rash, anemia, pyrexia, and fatigue. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

CYP3A Inhibitors and Inducers: Avoid concurrent use of BOSULIF with strong or moderate CYP3A inhibitors and inducers. (2.5, 2.6, 7.1, 7.2)

Proton Pump Inhibitors: May decrease bosutinib drug levels. Consider short-acting antacids in place of proton pump inhibitors. (7.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 9/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

*** Sections or subsections omitted from the Full Prescribing Information are not listed.**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The recommended dose and schedule of BOSULIF is 500 mg orally once daily with food. Continue treatment with BOSULIF until disease progression or patient intolerance.

If a dose is missed beyond 12 hours, the patient should skip the dose and take the usual prescribed dose on the following day.

2.2 Dose Escalation

Consider dose escalation to 600 mg once daily with food in patients who do not reach complete hematological response (CHR) by week 8 or a complete cytogenetic response (CCyR) by week 12, who did not have Grade 3 or higher adverse reactions, and who are currently taking 500 mg daily.

2.3 Dose Adjustments for Non-Hematologic Adverse Reactions

Elevated liver transaminases: If elevations in liver transaminases greater than 5×institutional upper limit of normal (ULN) occur, withhold BOSULIF until recovery to less than or equal to 2.5×ULN and resume at 400 mg once daily thereafter. If recovery takes longer than 4 weeks, discontinue BOSULIF. If transaminase elevations greater than or equal to 3×ULN occur concurrently with bilirubin elevations greater than 2×ULN and alkaline phosphatase less than 2×ULN (Hy's law case definition), discontinue BOSULIF *[see Warnings and Precautions (5.3)]*.

Diarrhea: For NCI CTCAE Grade 3-4 diarrhea (increase of greater than or equal to 7 stools/day over baseline/pretreatment), withhold BOSULIF until recovery to Grade less than or equal to 1. BOSULIF may be resumed at 400 mg once daily *[see Warnings and Precautions (5.1)]*.

For other clinically significant, moderate or severe non-hematological toxicity, withhold BOSULIF until the toxicity has resolved, then consider resuming BOSULIF at 400 mg once daily. If clinically appropriate, consider re-escalating the dose of BOSULIF to 500 mg once daily.

2.4 Dose Adjustments for Myelosuppression

Dose reductions for severe or persistent neutropenia and thrombocytopenia are described below (Table 1).

Table 1:
Dose Adjustments for Neutropenia and Thrombocytopenia

ANC[a] less than 1000×10^6/L or Platelets less than $50{,}000 \times 10^6$/L	Withhold BOSULIF until ANC greater than or equal to 1000×10^6/L and platelets greater than or equal to $50{,}000 \times 10^6$/L. Resume treatment with BOSULIF at the same dose if recovery occurs within 2 weeks. If blood counts remain low for greater than 2 weeks, upon recovery, reduce dose by 100 mg and resume treatment. If cytopenia recurs, reduce dose by an additional 100 mg upon recovery and resume treatment. Doses less than 300 mg/day have not been evaluated.

[a] Absolute Neutrophil Count

2.5 Concomitant Use With CYP3A Inhibitors

Avoid the concomitant use of strong or moderate CYP3A and/or P-gp inhibitors with BOSULIF as an increase in bosutinib plasma concentration is expected (strong CYP3A inhibitors include ritonavir, indinavir, nelfinavir, saquinavir, ketoconazole, boceprevir, telaprevir, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, nefazodone and conivaptan. Moderate CYP3A inhibitors include fluconazole, darunavir, erythromycin, diltiazem, atazanavir, aprepitant, amprenavir, fosamprevir, crizotinib, imatinib, verapamil, grapefruit products and ciprofloxacin) *[see Drug Interactions (7.1)]*.

2.6 Concomitant Use With CYP3A Inducers

Avoid the concomitant use of strong or moderate CYP3A inducers with BOSULIF as a large reduction in exposure is expected (strong CYP3A inducers include rifampin, phenytoin, carbamazepine, St. John's Wort, rifabutin and phenobarbital. Moderate CYP3A inducers include bosentan, nafcillin, efavirenz, modafinil and etravirine) *[see Drug Interactions (7.2)]*.

2.7 Hepatic Impairment

In patients with pre-existing mild, moderate, and severe hepatic impairment, the recommended dose of BOSULIF is 200 mg daily. A daily dose of 200 mg in patients with hepatic impairment is predicted to result in an area under the concentration curve

(AUC) similar to the AUC seen in patients with normal hepatic function receiving 500 mg daily. However, there are no clinical data for efficacy at the dose of 200 mg once daily in patients with hepatic impairment and CML *[see Use in Special Populations (8.6) and Clinical Pharmacology (12.3)]*.

2.8 Renal Impairment

In patients with pre-existing severe renal impairment (CLcr less than 30 mL/min), the recommended dose of BOSULIF is 300 mg daily. A daily dose of 300 mg in patients with severe renal impairment is predicted to result in an area under the concentration curve (AUC) similar to the AUC seen in patients with normal renal function receiving 500 mg daily. However, there are no clinical data for efficacy at the dose of 300 mg once daily in patients with severe renal impairment and CML *[see Use in Special Populations (8.7) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

100 mg tablets: yellow, oval, biconvex, film-coated tablets debossed with "Pfizer" on one side and "100" on the other.
500 mg tablets: red, oval, biconvex, film-coated tablets debossed with "Pfizer" on one side and "500" on the other.

4 CONTRAINDICATIONS

Hypersensitivity to BOSULIF. In the BOSULIF clinical trials, anaphylactic shock occurred in less than 0.2% of treated patients.

5 WARNINGS AND PRECAUTIONS

5.1 Gastrointestinal Toxicity

Diarrhea, nausea, vomiting, and abdominal pain occur with BOSULIF treatment. Monitor and manage patients using standards of care, including antidiarrheals, antiemetics, and/or fluid replacement. In the single-arm Phase 1/2 clinical trial, the median time to onset for diarrhea (all grades) was 2 days and the median duration per event was 1 day. Among the patients who experienced diarrhea, the median number of episodes of diarrhea per patient during treatment with BOSULIF was 3 (range 1-221). To manage gastrointestinal toxicity, withhold, dose reduce, or discontinue BOSULIF as necessary *[see Dosage and Administration (2.3) and Adverse Reactions (6)]*.

5.2 Myelosuppression

Thrombocytopenia, anemia and neutropenia occur with BOSULIF treatment. Patients with CML who are receiving BOSULIF should have a complete blood count performed weekly for the first month and then monthly thereafter, or as clinically indicated. To manage myelosuppression, withhold, dose reduce, or discontinue BOSULIF as necessary *[see Dosage and Administration (2.4) and Adverse Reactions (6)]*.

5.3 Hepatic Toxicity

One case consistent with drug induced liver injury (defined as concurrent elevations in ALT or AST greater than or equal to 3×ULN with total bilirubin greater than 2×ULN and alkaline phosphatase less than 2×ULN) occurred in a trial of BOSULIF in combination with letrozole. The patient recovered fully following discontinuation of BOSULIF. This case represented 1 out of 1209 patients in BOSULIF clinical trials.

In the 546 patients from the safety population, the incidence of ALT elevation was 17% and AST elevation was 14 %. Twenty percent of the patients experienced an increase in either ALT or AST. 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 30 and 33 days, respectively, and the median duration for each was 21 days.

Perform monthly hepatic enzyme tests for the first three months of treatment with BOSULIF and as clinically indicated. In patients with transaminase elevations, monitor liver enzymes more frequently. Withhold, dose reduce, or discontinue BOSULIF as necessary *[see Dosage and Administration (2.3) and Adverse Reactions (6)]*.

5.4 Fluid Retention

Fluid retention occurs with BOSULIF and may manifest as pericardial effusion, pleural effusion, pulmonary edema, and/or peripheral edema.

In the single-arm Phase 1/2 clinical trial in 546 patients with CML treated with prior therapy, severe fluid retention was reported in 14 patients (3%). Specifically, 9 patients had a Grade 3 or 4 pleural effusion, 3 patients experienced both Grade 3 or Grade 4 pleural and pericardial effusions, 1 patient experienced Grade 3 peripheral and pulmonary edema, and 1 patient had a Grade 3 edema.

Monitor and manage patients using standards of care. Interrupt, dose reduce or discontinue BOSULIF as necessary *[see Dosage and Administration (2.3) and Adverse Reactions (6)]*.

5.5 Embryofetal Toxicity

There are no adequate and well controlled studies of BOSULIF in pregnant women. BOSULIF can cause fetal harm when administered to a pregnant woman. Bosutinib caused embryofetal toxicities in rabbits at maternal exposures that were greater than the clinical exposure at the recommended bosutinib dose of 500 mg/day. Females of reproductive potential should be advised to avoid pregnancy while being treated with BOSULIF. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus *[see Use in Specific Populations (8.1)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Gastrointestinal toxicity *[see Dosage and Administration (2.3) and Warnings and Precautions (5.1)]*.
- Myelosuppression *[see Dosage and Administration (2.4) and Warnings and Precautions (5.2)]*.
- Hepatic toxicity *[see Dosage and Administration (2.5) and Warnings and Precautions (5.3)]*.
- Fluid retention *[see Warnings and Precautions (5.4)]*.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Serious adverse reactions reported include anaphylactic shock *[see Contraindications (4)]*, myelosuppression, gastrointestinal toxicity (diarrhea), fluid retention, hepatotoxicity and rash.

Adverse reactions of any toxicity grade reported for greater than 20% of patients in the Phase 1/2 safety population (n=546) were diarrhea (82%), nausea (46%), thrombocytopenia (41%), vomiting (39%), abdominal pain (37%), rash (35%), anemia (27%), pyrexia (26%), and fatigue (24%).

6.1 Imatinib-Resistant or -Intolerant Ph+ Chronic Phase (CP), Accelerated Phase (AP), and Blast Phase (BP) CML

The single-arm Phase 1/2 clinical trial enrolled patients with Ph+ chronic, accelerated, or blast phase chronic myelogenous leukemia (CML) and Ph+ acute lymphoblastic leukemia (ALL) with resistance or intolerance to prior therapy. The safety population (received at least 1 dose of BOSULIF) included 546 CML patients. Within the safety population there were 287 patients with CP CML previously treated with imatinib only who had a median duration of BOSULIF treatment of 24 months, and a median dose intensity of 484 mg/day. There were 119 patients with CP CML previously treated with both imatinib and at least 1 additional TKI who had a median duration of BOSULIF treatment of 9 months and a median dose intensity of 475 mg/day. There were 76 patients with AP CML, and 64 patients with BP CML. In the patients with AP CML and BP CML, the median duration of BOSULIF treatment was 10 months and 3 months, respectively. The median dose intensity was 483 mg/day, and 500 mg/day, in the AP CML and BP CML cohorts, respectively.

Table 2 identifies adverse reactions greater than or equal to 10% for all grades and grades 3 or 4 for the Phase 1/2 CML safety population.

Table 2:
Adverse Reactions (10% or greater) in patients with CML

System Organ Class Preferred Term	CP CML N=406 n (%)		AdvP CML N=140 n (%)		All CP and AdvP CML N=546 n (%)	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Gastrointestinal Disorders						
Diarrhea	342 (84)	38 (9)	107 (76)	7 (5)	449 (82)	45 (8)
Nausea	186 (46)	5 (1)	66 (47)	3 (2)	252 (46)	8 (1)
Abdominal Pain[a]	162 (40)	6 (1)	41 (29)	7 (5)	203 (37)	13 (2)
Vomiting	152 (37)	12 (3)	59 (42)	5 (4)	211 (39)	17 (3)
Blood and Lymphatic System Disorders						
Thrombocytopenia	163 (40)	105 (26)	59 (42)	52 (37)	222 (41)	157 (29)
Anemia	94 (23)	35 (9)	52 (37)	37 (26)	146 (27)	72 (13)
Neutropenia	65 (16)	43 (11)	26 (19)	25 (18)	91 (17)	68 (12)
General Disorders and Administrative Site Conditions						
Fatigue[b]	104 (26)	6 (1)	28 (20)	6 (4)	132 (24)	12 (2)
Pyrexia	90 (22)	2 (<1)	51 (36)	4 (3)	141 (26)	6 (1)
Edema[c]	56 (14)	1 (<1)	19 (14)	1 (1)	75 (14)	2 (<1)
Asthenia	45 (11)	5 (1)	14 (10)	1 (1)	59 (11)	6 (1)
Infections and Infestations						
Respiratory tract infection[d]	49 (12)	2 (<1)	14 (10)	0	63 (12)	2 (<1)
Nasopharyngitis	47 (12)	0	7 (5)	0	54 (10)	0
Investigations						
Alanine aminotransferase increased	81 (20)	30 (7)	14(10)	7(5)	95(17)	37(7)
Aspartate aminotransferase increased	64 (16)	15 (4)	15(11)	4 (3)	79(14)	19(3)
Metabolism and nutrition disorder						
Decreased appetite	53 (13)	3 (1)	19 (14)	0	72 (13)	3 (1)
Musculoskeletal and Connective Tissue Disorder						
Arthralgia	58 (14)	2 (<1)	18 (13)	0	76 (14)	2 (<1)
Back pain	49 (12)	3 (1)	10 (7)	2 (1)	59 (11)	5 (1)
Nervous System Disorders						
Headache	82 (20)	3 (1)	25 (18)	6 (4)	107 (20)	9 (2)
Dizziness	39 (10)	0	18 (13)	1 (1)	57 (10)	1 (<1)
Respiratory, Thoracic and Mediastinal Disorders						
Dyspnea	41 (10)	4 (1)	26 (19)	8 (6)	67 (12)	12 (2)

System Organ Class Preferred Term	CP CML N=406 n (%)		AdvP CML N=140 n (%)		All CP and AdvP CML N=546 n (%)	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Cough	80(20)	0	30(21)	0	110(20)	0
Skin and Subcutaneous Disorders						
Rash[e]	140 (34)	32 (8)	49 (35)	6 (4)	189 (35)	38 (7)
Pruritus	43 (11)	3 (1)	11 (8)	0	54 (10)	3 (1)

CP CML = Chronic Phase CML; AdvP CML = Advanced Phase CML (includes patients with Accelerated Phase and Blast Phase CML)
[a] Abdominal pain includes the following preferred terms: Abdominal pain, Abdominal pain upper, Abdominal pain lower, Abdominal tenderness, Gastrointestinal pain, Abdominal discomfort
[b] Fatigue includes the following preferred terms: Fatigue, Malaise
[c] Edema includes the following preferred terms: Edema, Edema peripheral, Localized edema, Face edema
[d] Respiratory tract infection includes the following preferred terms: Respiratory tract infection, Upper respiratory tract infection, Lower respiratory tract infection, Viral upper respiratory tract infection, Respiratory tract infection viral
[e] Rash includes the following preferred terms: Rash, Rash macular, Rash pruritic, Rash generalized, Rash papular, Rash maculo-papular

In the single-arm Phase 1/2 clinical trial, one patient (0.2%) experienced QTcF interval of greater than 500 ms. Patients with uncontrolled or significant cardiovascular disease including QT interval prolongation were excluded by protocol.

Table 3 identifies the clinically relevant or severe Grade 3/4 laboratory test abnormalities for the Phase 1/2 CML safety population.

Table 3:
Number (%) of Patients with Clinically Relevant or Severe Grade 3/4 Laboratory Test Abnormalities In the Phase 1/2 Clinical Study, Safety Population

	CP CML N=406 n (%)	AdvP CML N=140 n (%)	All CP and AdvP CML N=546 n (%)
Hematology Parameters			
Platelet Count (Low) less than 50×10^9/L	102 (25)	80 (57)	182 (33)
Absolute Neutrophil Count less than 1×10^9/L	74 (18)	52 (37)	126 (23)
Hemoglobin (Low) less than 80 g/L	53 (13)	49 (35)	102 (19)
Biochemistry Parameters			
SGPT/ALT greater than 5.0×ULN	39 (10)	8 (6)	47 (9)
SGOT/AST greater than 5.0×ULN	17 (4)	4 (3)	21 (4)
Lipase greater than 2×ULN	33 (8)	4 (3)	37 (7)
Phosphorus (Low) less than 0.6 mmol/L	30 (7)	10 (7)	40 (7)
Total Bilirubin greater than 3.0×ULN	3 (1)	2 (1)	5 (1)

6.2 Additional Data from Multiple Clinical Trials

The following adverse reactions were reported in patients in clinical trials with BOSULIF (less than 10% of BOSULIF-treated patients). They represent an evaluation of the adverse reaction data from 870 patients with Ph+ leukemia who received at least 1 dose of single-agent BOSULIF. These adverse reactions are presented by system organ class and are ranked by frequency. These adverse reactions are included based on clinical relevance and ranked in order of decreasing seriousness within each category.

Blood and Lymphatic System Disorders: *1% and less than 10%* - febrile neutropenia

Cardiac Disorders: *1% and less than 10%* - pericardial effusion; *0.1% and less than 1%* - pericarditis

Ear and Labyrinth Disorders: *1% and less than 10%* - tinnitus

Gastrointestinal Disorders: *1% and less than 10%* - gastritis; *0.1% and less than 1%* - acute pancreatitis, gastrointestinal hemorrhage[a]

General Disorders and Administrative Site Conditions: *1% and less than 10%* - chest pain[b], pain

Hepatobiliary Disorders: *1% and less than 10%* - hepatotoxicity[c], abnormal hepatic function[d]; *0.1% and less than 1%* - liver injury

Immune System Disorders: *1% and less than 10%* - drug hypersensitivity; *0.1% and less than 1%* - anaphylactic shock

Infections and Infestations: *1% and less than 10%* - pneumonia[e], influenza, bronchitis

Investigations: *1% and less than 10%* - electrocardiogram QT prolonged, increased blood creatine phosphokinase, increased blood creatinine

Metabolism and Nutrition Disorder: *1% and less than 10%* - hyperkalemia, dehydration

Musculoskeletal and Connective Tissue Disorder: *1% and less than 10%* - myalgia

Nervous System Disorders: *1% and less than 10%* - dysgeusia

Renal and Urinary Disorders: *1% and less than 10%* - acute renal failure, renal failure

Respiratory, Thoracic and Mediastinal Disorders: *1% and less than 10%* - pleural effusion; *0.1% and less than 1%* - acute pulmonary edema, respiratory failure, pulmonary hypertension

Skin and Subcutaneous Disorders: *1% and less than 10%* - urticaria, pruritus, acne; *0.1% and less than 1%* - erythema multiforme, exfoliative rash, drug eruption

[a] Gastrointestinal hemorrhage includes the following preferred terms: gastrointestinal hemorrhage, gastric hemorrhage, upper gastrointestinal hemorrhage
[b] Chest pain includes the following preferred terms: chest pain, chest discomfort
[c] Hepatotoxicity includes the following preferred terms: hepatotoxicity, toxic hepatitis, cytolytic hepatitis
[d] Abnormal hepatic function includes the following preferred terms: abnormal hepatic function, liver disorder
[e] Pneumonia includes the following preferred terms: pneumonia, bronchopneumonia, lobar pneumonia, primary atypical pneumonia

7 DRUG INTERACTIONS

7.1 Drugs That May Increase Bosutinib Plasma Concentrations

CYP3A or P-glycoprotein (P-gp) inhibitors: Avoid the concomitant use of strong or moderate CYP3A and/or P-gp inhibitors with BOSULIF as an increase in bosutinib plasma concentration is expected *[see Dosage and Administration (2.5)]*. In a dedicated cross-over drug-interaction trial in healthy volunteers (N=24), concomitant ketoconazole (strong CYP3A inhibitor) increased bosutinib C_{max} 5.2-fold and AUC 8.6-fold compared to BOSULIF alone *[see Clinical Pharmacology (12.3)]*.

7.2 Drugs That May Decrease Bosutinib Plasma Concentrations

CYP3A Inducers: Avoid the concomitant use of strong or moderate CYP3A inducers with BOSULIF as a large reduction in exposure is expected *[see Dosage and Administration (2.6)]*. In a dedicated cross-over drug-interaction trial in healthy volunteers (N=24), concomitant rifampin (strong CYP3A inducer) decreased bosutinib C_{max} by 86% and AUC by 94% compared to BOSULIF alone *[see Clinical Pharmacology (12.3)]*.

Proton Pump Inhibitors: In a dedicated cross-over drug-interaction trial in healthy volunteers (N=24), concomitant lansoprazole (PPI) decreased bosutinib C_{max} by 46% and AUC by 26% compared to BOSULIF alone *[see Clinical Pharmacology (12.3)]*.

Consider using short-acting antacids or H2 blockers instead of PPIs to avoid a reduction in bosutinib exposure. Separate antacid or H2 blocker dosing and BOSULIF dosing by more than 2 hours.

7.3 Drugs That May Have Their Plasma Concentrations Altered By Bosutinib

Substrates of P-glycoprotein: An *in vitro* study suggests that BOSULIF may have the potential to increase the plasma concentrations of drugs that are P-gp substrates, such as digoxin *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D [see Warnings and Precautions (5.5)]

Based on its mechanism of action and findings in animals, BOSULIF can cause fetal harm when administered to a pregnant woman. Studies in animals showed reproductive toxicities. If BOSULIF is used during pregnancy, or if the patient becomes pregnant while taking BOSULIF, the patient should be apprised of the potential hazard to the fetus.

Fetal exposure to bosutinib-derived radioactivity during pregnancy was demonstrated in a placental-transfer study in pregnant rats. Bosutinib was administered orally to pregnant rats during the period of organogenesis at doses of 1, 3 and 10 mg/kg/day. This study did not expose pregnant rats to enough bosutinib to fully evaluate adverse outcomes.

In a study conducted in rabbits, bosutinib was administered orally to pregnant animals during the period of organogenesis at doses of 3, 10 and 30 mg/kg/day. At the maternally-toxic dose of 30 mg/kg/day of bosutinib, there were fetal anomalies (fused sternebrae, and two fetuses had various visceral observations), and an approximate 6% decrease in fetal body weight. The dose of 30 mg/kg/day resulted in exposures (AUC) approximately 4 times those in humans at the 500 mg/day dose of bosutinib.

8.3 Nursing Mothers

It is not known whether bosutinib is excreted in human milk. Bosutinib and/or its metabolites were excreted in the milk of lactating rats. Radioactivity was present in the plasma of suckling offspring 24 to 48 hours after lactating rats received a single oral dose of radioactive bosutinib. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from BOSULIF, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and efficacy of BOSULIF in patients less than 18 years of age have not been established.

8.5 Geriatric Use

In the Phase 1/2 clinical trial of BOSULIF in patients with Ph+ CML, 20% were age 65 and over, 4% were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment

Treat with a dose of 200 mg daily in patients with any baseline hepatic impairment. In a dedicated hepatic impairment trial, the exposure to bosutinib increased (C_{max} increased 1.5- to 2.3-fold and the AUC increased 1.9- to 2.4-fold) in patients with hepatic impairment (Child-Pugh classes A, B, and C; N=18) compared to matched healthy volunteers (N=9) *[see Dosage and Administration (2.7), Adverse Reactions (6), and Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

Reduce the BOSULIF dose in patients with CLcr less than 30 mL/min at baseline. For patients with CLcr 30 to 50 mL who cannot tolerate a 500 mg dose, follow dose adjustment recommendations for toxicity. In a dedicated renal impairment trial, compared to volunteers with normal renal function, the exposure (AUC) of bosutinib increased by 60% and 35% in subjects with CLcr less than 30 mL/min and CLcr 30 to 50 mL/min, respectively *[see Dosing and Administration (2.8) and Clinical Pharmacology (12.3)]*.

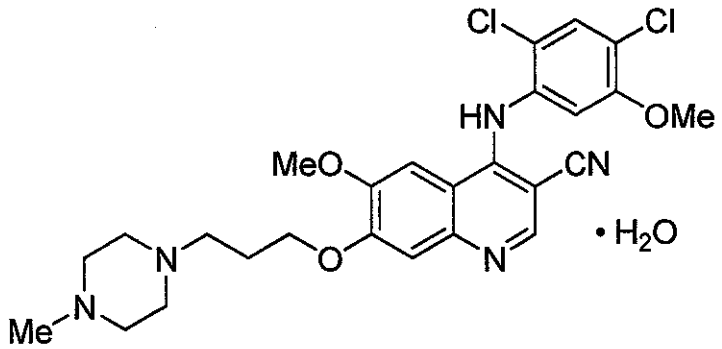
BOSULIF has not been studied in patients undergoing hemodialysis.

10 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.

11 DESCRIPTION

Bosutinib is a kinase inhibitor. The chemical name for bosutinib monohydrate is 3-Quinolinecarbonitrile, 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(4-methyl-1-piperazinyl) propoxy]-, hydrate (1:1). Its chemical formula is $C_{26}H_{29}Cl_2N_5O_3 \bullet H_2O$ (monohydrate); its molecular weight is 548.46 (monohydrate), equivalent to 530.46 (anhydrous). Bosutinib monohydrate has the following chemical structure:



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 monohydrate behaves as a highly soluble compound. Above pH 5, the solubility of bosutinib monohydrate reduces rapidly.

BOSULIF® (bosutinib) tablets are supplied for oral administration in two strengths: a 100 mg yellow, oval, biconvex, film-coated tablet debossed with "Pfizer" on one side and "100" on the other; and a 500 mg red, oval, biconvex, film-coated tablet debossed with "Pfizer" on one side and "500" on the other.

Each 100 mg BOSULIF tablet contains 103.40 mg of bosutinib monohydrate, equivalent to 100 mg of bosutinib; each 500 mg BOSULIF tablet contains 516.98 mg of bosutinib monohydrate, equivalent to 500 mg of bosutinib. The following inactive ingredients are included in the tablets: 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).

PATIENT INFORMATION
BOSULIF® (BAH-su-lif)
(bosutinib)
tablets

Read the Patient Information that comes with BOSULIF before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or treatment.

What is BOSULIF?

BOSULIF is a prescription medicine used to treat adults who have a certain type of leukemia called Philadelphia chromosome-positive chronic myelogenous leukemia (Ph+ CML) who no longer benefit from or did not tolerate other treatment.

It is not known if BOSULIF is safe and effective in children less than 18 years of age.

Who should not take BOSULIF?

Do not take BOSULIF if you are allergic to bosutinib or any of the ingredients in BOSULIF. See the end of this leaflet for a complete list of ingredients of BOSULIF.

What should I tell my doctor before taking BOSULIF?

Before you take BOSULIF, tell your doctor if you:

- have liver problems
- have heart problems
- have kidney problems
- have any other medical conditions
- are pregnant or plan to become pregnant. BOSULIF can harm your unborn baby. You should not become pregnant while taking BOSULIF. Tell your doctor right away if you become pregnant while taking BOSULIF.
- are a woman who may become pregnant. Use effective contraception (birth control) during and for at least 30 days after completing treatment with BOSULIF. Talk to your doctor about forms of birth control.
- are breastfeeding or plan to breastfeed. It is not known if BOSULIF passes into your breast milk or if it can harm your baby. You and your doctor should decide if you will take BOSULIF or breastfeed. You should not do both.

Tell your doctor about the medicines you take, including prescription medicines, non-prescription medicines, vitamins, and herbal supplements. BOSULIF and certain other medicines can affect each other.

Especially tell your doctor if you take:

- **medicines that increase the amount of BOSULIF in your blood stream, such as:**
  - amprenavir (Agenerase®)
  - aprepitant (Emend®)
  - atazanavir (Reyataz®)
  - boceprevir (Victrelis®)
  - ciprofloxacin (Cipro®, Proquin XR®)

Tell your doctor right away if you get respiratory tract infections, loss of appetite, headache, dizziness, back pain, joint pain, or itching while taking BOSULIF. These may be symptoms of a severe allergic reaction.

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

These are not all of the possible side effects of BOSULIF. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store BOSULIF?

- Store BOSULIF between 68°F to 77°F (20°C to 25°C).
- Ask your doctor or pharmacist about the right way to throw away outdated or unused BOSULIF.

Keep BOSULIF and all medicines out of the reach of children.

General information about BOSULIF:

Medicines are sometimes prescribed for purposes other than those listed in the Patient Information leaflet. Do not use BOSULIF for a condition for which it is not prescribed. Do not give BOSULIF to other people even if they have the same symptoms you have. It may harm them.

This Patient Information leaflet summarizes the most important information about BOSULIF. If you would like more information, talk with your doctor. You may ask your doctor or pharmacist for information about BOSULIF that is written for healthcare professionals.

For more information, go to **www.Bosulif.com** or **www.pfizermedicalinformation.com** or call **1-800-438-1985.**

What are the ingredients in BOSULIF?

Active ingredient: bosutinib.
Inactive ingredients: 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).

This Patient Information has been approved by the U.S. Food and Drug Administration.

Distributed by
Pfizer Labs
Division of Pfizer Inc, NY, NY 10017

LAB-0639-3.0
Revised: September 2013