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, Recommended Starting Dosage with Hepatic Impairment or Renal Impairment (2.7)	11/2014
Warnings and Precautions, Renal Toxicity (5.5)	11/2014

----------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)

----------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)
- Renal Toxicity Monitor patients for renal function at baseline and during therapy with BOSULIF (5.5)
- Embryofetal Toxicity: May cause fetal harm. Females of reproductive potential should avoid becoming pregnant while being treated with BOSULIF. (5.6)

----------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: 11/2014

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 $1000x10^6$/L or Platelets less than $50,000x10^6$/L	Withhold BOSULIF until ANC greater than or equal to$1000x10^6$/L and platelets greater than or equal to $50,000x10^6$/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 Recommended Starting Dosage with Hepatic Impairment or Renal Impairment

Organ Function Status	Recommended Starting Dosage
Normal hepatic and renal function	500 mg once daily
Hepatic impairment	
Mild (Child-Pugh A), Moderate (Child-Pugh B) or severe (Child-Pugh C)	200 mg daily
Renal impairment	
Creatinine clearance 30 to 50 mL/min	400 mg daily
Creatinine clearance less than 30 mL/min	300 mg daily
[see Use in Specific Populations (8.6,8.7) 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 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. Perform complete blood counts weekly for the first month of therapy 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 hepatic enzyme tests monthly for the first three months of BOSULIF treatment 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 Renal Toxicity

An on-treatment decline in estimated glomerular filtration rate (eGFR) has occurred in patients treated with BOSULIF. Table 2 identifies the shift from baseline to lowest observed estimated glomerular filtration rate (eGFR) during BOSULIF therapy for patients in the global Ph+ Leukemia studies. The median duration of therapy with BOSULIF was approximately 17 months (range, 0.03 to 95) for patients in these studies.

Table 2:
Shift from Baseline to Lowest Observed eGFR Group During Treatment
Safety Population in Clinical Studies
(n=818)*

Baseline		Follow Up					
Renal Function Status	n	Normal n (%)	Mild n (%)	Mild to Moderate n (%)	Moderate to Severe n (%)	Severe n (%)	Kidney Failure n (%)
Normal	274	53 (19)	174 (64)	30 (11)	14 (5)	1 (<1)	1 (<1)
Mild	438	10 (2)	170 (39)	177 (40)	63 (14)	14 (3)	2 (1)
Mild to Moderate	79	0	4 (5)	28 (35)	37 (47)	10 (13)	0
Moderate to Severe	24	0	1 (4)	1 (4)	6 (25)	15 (63)	1 (4)
Severe	1	0	0	0	0	0	1 (100)
Total	816	63 (8)	349 (43)	236 (29)	120 (15)	40 (5)	5 (1)

Notes: Grading is based on Modification in Diet in Renal Disease method (MDRD).
KDIGO Classification by eGFR: Normal: greater than or equal to 90, Mild: 60 to less than 90, Mild to Moderate: 45 to less than 60, Moderate to Severe: 30 to less than 45, Severe: 15 to less than 30, Kidney Failure: less than 15 ml/min/1.73 m^2.
*Among the 818 patients, eGFR was missing in 5 patients at baseline or on-therapy. There were no patients with kidney failure at baseline.

Monitor renal function at baseline and during therapy with BOSULIF, with particular attention to those patients who have preexisting renal impairment or risk factors for renal dysfunction. Consider dose adjustment in patients with baseline and treatment emergent renal impairment *[see Dosage and Administration (2.7)]*.

5.6 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)]*.
- Renal toxicity *[see Warnings and Precautions (5.5)]*.

6.1 Clinical Trials Experience

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%) *[see Clinical Studies (14)]*.

Adverse Reactions in Patients with Imatinib-Resistant or -Intolerant Ph+ Chronic Phase (CP), Accelerated Phase (AP), and Blast Phase (BP) CML

The single-arm Phase 1/2 clinical trial (Study 1) enrolled patients with Ph+ chronic, accelerated, or blast phase chronic myelogenous leukemia (CML) and with resistance or intolerance to prior therapy *[see Clinical Studies (14)]*. The safety population (received at least 1 dose of BOSULIF) included 546 CML patients:

- 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.
- 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.
- 140 patients with advanced phase CML including 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 3 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 3:
Adverse Reactions (10% or Greater) in Patients with CML in Study 1

	Chronic Phase CML N=406		Advanced Phase CML N=140	
	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
Diarrhea	84	9	76	5
Nausea	46	1	47	2
Abdominal Pain[a]	40	1	29	5
Thrombocytopenia	40	26	42	37
Vomiting	37	3	42	4
Rash[b]	34	8	35	4
Fatigue[c]	26	1	20	4
Anemia	23	9	37	26
Pyrexia	22	<1	36	3
Increased alanine aminotransferase	20	7	10	5
Headache	20	1	18	4
Cough	20	0	21	0
Increased aspartate aminotransferase	16	4	11	3
Neutropenia	16	11	19	18
Edema[d]	14	<1	14	1

	Chronic Phase CML N=406		Advanced Phase CML N=140	
	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
Arthralgia	14	<1	13	0
Decreased appetite	13	1	14	0
Respiratory tract infection[e]	12	<1	10	0
Nasopharyngitis	12	0	5	0
Back pain	12	1	7	1
Asthenia	11	1	10	1
Pruritus	11	1	8	0
Dizziness	10	0	13	1
Dyspnea	10	1	19	6

Advanced Phase CML includes patients with Accelerated Phase and Blast Phase CML
[a] Abdominal pain includes the following terms: abdominal pain, upper abdominal pain, lower abdominal pain, abdominal tenderness, gastrointestinal pain, abdominal discomfort
[b] Rash includes the following terms: rash, macular rash, pruritic rash, generalized rash, popular rash, maculo-papular rash
[c] Fatigue includes the following terms: fatigue, malaise
[d] Edema includes the following terms: edema, peripheral edema, localized edema, face edema
[e] Respiratory tract infection includes the following terms: respiratory tract infection, upper respiratory tract infection, lower respiratory tract infection, viral upper respiratory tract infection, viral respiratory tract infection

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

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

Table 4:
Number (%) of Patients with Clinically Relevant or Severe Grade 3/4 Laboratory Test Abnormalities in Patients with CML in Study 1, Safety Population

	Chronic Phase CML N=406 n (%)	Advanced Phase 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)

Additional Adverse Reactions 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 (includes gastrointestinal hemorrhage, gastric hemorrhage, upper gastrointestinal hemorrhage)

General Disorders and Administrative Site Conditions: *1% and less than 10%* - chest pain (includes chest pain and chest discomfort), pain

Hepatobiliary Disorders: *1% and less than 10%* - hepatotoxicity (includes hepatotoxicity, toxic hepatitis, and cytolytic hepatitis), abnormal hepatic function (includes abnormal hepatic function, liver disorder); *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 (includes pneumonia, bronchopneumonia, lobar pneumonia, primary atypical pneumonia), 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

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 (5.6)]

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 starting dose in patients with severe (CLcr less than 30 mL/min) or moderate (CLcr 30 to 50 mL/min) renal impairment at baseline. For patients who have declining renal function while on BOSULIF who cannot tolerate a 500 mg dose, follow dose adjustment recommendations for toxicity. In a dedicated renal impairment trial, compared to subjects 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, compared to subjects with normal renal function *[see Dosing and Administration (2.7) and Clinical Pharmacology (12.3)]*.

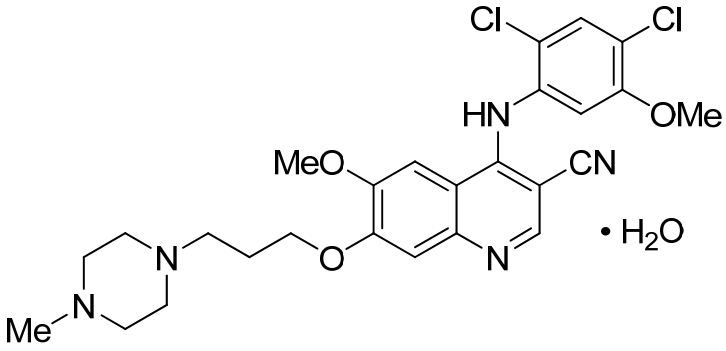
BOSULIF has not been studied in patients undergoing hemodialysis.

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 $C_{26}H_{29}Cl_2N_5O_3 \cdot H_2O$ (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).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Bosutinib is a tyrosine kinase inhibitor. Bosutinib inhibits the Bcr-Abl kinase that promotes CML; it is also an inhibitor of Src-family kinases including Src, Lyn, and Hck. Bosutinib inhibited 16 of 18 imatinib-resistant forms of Bcr-Abl expressed in murine myeloid cell lines. Bosutinib did not inhibit the T315I and V299L mutant cells. In mice, treatment with bosutinib reduced the size of CML tumors relative to controls and inhibited growth of murine myeloid tumors expressing several imatinib-resistant forms of Bcr-Abl.

12.2 Pharmacodynamics

The effect of a single dose of bosutinib 500 mg alone and with ketoconazole on the QTc interval was evaluated in a randomized, placebo- and active-controlled (moxifloxacin 400 mg) two or three-period crossover thorough QT study in 60 healthy subjects. No significant changes in placebo adjusted, baseline-corrected QTc were observed.

12.3 Pharmacokinetics

Absorption

Following administration of a single dose of BOSULIF 500 mg with food in patients with cancer, the median time-to-peak concentration (t_{max}) was 4-6 hours. Bosutinib exhibits dose proportional increases in AUC and C_{max}, over the dose range of 200 to 800 mg. After 15 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. When given with a high fat meal, the C_{max} and AUC of bosutinib increased 1.8- and 1.7-fold, respectively.

Distribution

After administration of a single dose of BOSULIF 500 mg with food in patients with CML, bosutinib had a mean apparent volume of distribution ± standard deviation of 6080 ± 1230 L.

Bosutinib was highly bound to human plasma proteins *in vitro* (94%) and *ex vivo* in healthy subjects (96%), and binding was not concentration-dependent. Bosutinib is a P-gp substrate and inhibitor *in vitro*. No studies have been conducted with other transporters.

Metabolism

Bosutinib is primarily metabolized by CYP3A4. The major circulating metabolites identified in plasma are oxydechlorinated (M2) bosutinib (19% of parent exposure) and *N*-desmethylated (M5) bosutinib (25% of parent exposure), with bosutinib *N*-oxide (M6) as a minor circulating metabolite. All the metabolites were deemed inactive.

Elimination

In patients with CML given single oral doses of BOSULIF 500 mg with food, the mean terminal phase elimination half-life ($t_{1/2}$) was 22.5 (1.7) hours, and the mean (SD) clearance (Cl/F) was 189 (48) L/h. In six healthy male subjects given a single oral dose of [^{14}C] radiolabeled bosutinib, 91.3% of the dose was recovered in feces and 3% of the dose recovered in urine.

Hepatic Impairment

In a dedicated hepatic impairment trial, a single dose of BOSULIF 200 mg was administered with food to 18 volunteers with hepatic impairment (Child-Pugh classes A, B, and C) and 9 matched healthy volunteers. C_{max} of bosutinib increased 2.4-fold, 2-fold, and 1.5-fold, respectively, in Child-Pugh classes A, B, and C, and bosutinib AUC increased 2.3-fold, 2-fold, and 1.9-fold, respectively *[see Dosage and Administration (2.7), and Use in Specific Populations (8.6)]*.

Renal Impairment

In a dedicated renal impairment trial, a single dose of BOSULIF 200 mg was administered with food to 26 subjects with mild (CLcr: 51 to 80 mL/min), moderate (CLcr: 30 to 50 mL/min) or severe renal impairment (CLcr less than 30 mL/min) and to 8 subjects with normal renal function. Creatinine Clearance for category classification was calculated by the Cockcroft-Gault formula. Subjects with moderate and severe renal impairment had a 35% and 60% increase in AUC compared to subjects with normal renal function, respectively. Bosutinib exposure was not changed in subjects with mild renal impairment. The BOSULIF dose should be reduced in patients with severe (CLcr less than 30 mL/min) or moderate (CLcr between 30 to 50 mL/min) renal impairment *[see Dosage and Administration (2.1) and Use in Specific Populations (8.7)]*.

Drug Interactions

CYP3A Inhibitors

In a cross-over trial of 24 healthy volunteers, a single dose of 100 mg of BOSULIF was either administered alone or in combination with five daily doses of 400 mg of ketoconazole under fasting conditions. Ketoconazole increased bosutinib C_{max} and AUC 5.2-fold and 8.6-fold, respectively *[see Dosage and Administration (2.5) and Drug Interactions (7.1)]*.

CYP3A Inducers

In a cross-over trial of 24 healthy volunteers, a single dose of 500 mg of BOSULIF was either administered alone or in combination with six daily doses of 600 mg of rifampin under fed conditions. Rifampin decreased bosutinib C_{max} and AUC by 86% and 94%, respectively *[see Dosage and Administration (2.5) and Drug Interactions (7.2)]*.

P-gp Substrates

An *in vitro* study suggests that BOSULIF has the potential to increase the plasma concentrations of drugs that are P-gp substrates. The estimated I/IC_{50} was 0.19, when considering the C_{max} at the 500 mg dose of BOSULIF.

pH Altering Medications

BOSULIF displays pH-dependent aqueous solubility, *in vitro.* In a cross-over trial in 24 healthy volunteers, a single oral dose of 400 mg of BOSULIF was either administered alone or in combination with multiple-oral doses of 60 mg of lansoprazole under fasting conditions. Lansoprazole decreased bosutinib C_{max} and AUC by 46% and 26%, respectively.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A 2-year carcinogenicity study was conducted orally in rats at bosutinib doses up to 25 mg/kg/day in males and 15 mg/kg/day in females. The exposures achieved at the high dose were approximately 1.5- to 3-fold the human exposure (based on AUC) at the bosutinib dose of 500 mg/day. The study was negative for carcinogenic findings.

Bosutinib was not mutagenic or clastogenic in a battery of tests, including the bacteria reverse mutation assay (Ames Test), the *in vitro* assay using human peripheral blood lymphocytes and the micronucleus test in orally treated

male mice.

In a rat fertility study, drug-treated males were mated with untreated females, or untreated males were mated with drug-treated females. Females were administered the drug from pre-mating through early embryonic development. The dose of 70 mg/kg/day of bosutinib resulted in reduced fertility in males as demonstrated by 16% reduction in the number of pregnancies. There were no lesions in the male reproductive organs at this dose. This dose of 70 mg/kg/day resulted in exposure (AUC) in male rats approximately equal to that in humans at the 500 mg/day dose of bosutinib. Fertility (number of pregnancies) was not affected when female rats were treated with bosutinib. However, there were increased embryonic resorptions at greater than or equal to 10 mg/kg/day of bosutinib (40% of the human exposure), and decreased implantations and reduced number of viable embryos at 30 mg/kg/day of bosutinib (1.4 times the human exposure).

14 CLINICAL STUDIES

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

A single-arm, Phase 1/2 open-label, multicenter trial (Study 1) 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 previously treated with one prior TKI (imatinib) or more than one TKI (imatinib followed by dasatinib and/or nilotinib). The definition of imatinib resistance included (1) failure to achieve or maintain any hematologic improvement within four weeks; (2) failure to achieve a complete hematologic response (CHR) by 3 months, cytogenetic response by 6 months or major cytogenetic response (MCyR) by 12 months; (3) progression of disease after a previous cytogenetic or hematologic response; or (4) 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 protocol was amended to exclude patients with a known history of the T315I mutation after 396 patients were enrolled in the trial.

The efficacy endpoints for patients with CP CML previously treated with one prior TKI (imatinib) were the rate of attaining MCyR at week 24 and the duration of MCyR. The efficacy endpoints for patients with CP CML previously treated with both imatinib and at least 1 additional TKI were the cumulative rate of attaining MCyR by week 24 and the duration of MCyR. The efficacy endpoints for patients with previously treated AP and BP CML were confirmed complete hematologic response (CHR) and overall hematologic response (OHR).

The trial enrolled 546 patients with CP, AP or BP CML. Of the total patient population 73% were imatinib resistant and 27% were imatinib intolerant. In this trial, 53% of patients were males, 65% were Caucasian, and 20% were 65 years old or older. Of the 546 treated patients, 503 were considered evaluable for efficacy. Patients were evaluable for efficacy if they had received at least one dose of BOSULIF and had a valid baseline efficacy assessment. Among evaluable patients, there were 266 patients with CP CML previously treated with one prior TKI (imatinib), 108 patients with CP CML previously treated with both imatinib and at least 1 additional TKI, and 129 patients with advanced phase CML previously treated with at least one TKI.

Median duration of BOSULIF treatment was 22 months in patients with CP CML previously treated with one TKI (imatinib), 8 months in patients with CP CML previously treated with imatinib and at least 1 additional TKI, 10 months in patients with AP CML previously treated with at least imatinib, and 3 months in patients with BP CML previously treated with at least imatinib.

The 24 week efficacy results are present in Table 5.

Table 5:
Efficacy Results in Patients with Ph+ CP CML with Resistance to or Intolerance to Imatinib

	Prior Treatment with Imatinib Only (N=266 evaluable) n (%) at 24 Weeks	**Prior Treatment with Imatinib and Dasatinib or Nilotinib (N=108 evaluable) n (%) by 24 Weeks**
Week 24		
MCyR	90 (33.8)	29 (26.9)
(95% CI)	(28.2, 39.9)	(18.8, 36.2)

Abbreviations: CI = confidence interval, MCyR = major cytogenetic response

The minimum follow-up was 23 months for patients with CP CML treated with one prior TKI (imatinib) and 13 months for patients with CP CML treated with imatinib and at least one additional TKI. For the 53.4% of patients with CP CML treated with one prior TKI (imatinib) who achieved a MCyR at any time, the median duration of MCyR was not reached. Among these patients, 52.8% had a MCyR lasting at least 18 months. For the 32.4% of patients with CP CML treated with imatinib and at least one additional TKI who achieved a MCyR at any time, the median duration of MCyR was not reached. Among these patients, 51.4% had a MCyR lasting at least 9 months. Of the 374 evaluable patients with CP CML, 16 patients had confirmed disease transformation to AP or BP while on treatment with BOSULIF.

The 48 week efficacy results in patients with accelerated and blast phases CML previously treated with at least imatinib are summarized in Table 6.

Table 6:
Efficacy Results in Patients with Accelerated Phase and Blast Phase CML Previously Treated with at Least Imatinib

	AP CML (N=69 evaluable) n (%)	**BP CML (N=60 evaluable) n (%)**
CHR[a] by Week 48 (95% CI)	21 (30.4) 19.9, 42.7)	9 (15) (7.1, 26.6)
OHR[a] by Week 48 (95% CI)	38 (55.1) (42.6, 67.1)	17 (28.3) (17.5, 41.4)

Abbreviations: CI = confidence interval, OHR = overall hematologic response, CHR = complete hematologic response

[a.] 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 less than or equal to institutional ULN, platelets greater than or equal to 100,000/mm^3 and less than 450,000/mm^3, absolute neutrophil count (ANC) greater than or equal to 1.0×10^9 /L, no blasts or promyelocytes in peripheral blood, less than 5% myelocytes + metamyelocytes in bone marrow, less than 20% basophils in peripheral blood, and no extramedullary involvement. No evidence of leukemia (NEL): Meets all other criteria for CHR except may have thrombocytopenia (platelets greater than or equal to 20,000/mm^3 and less than 100,000/mm^3) and/or neutropenia (ANC greater than or equal to 0.5×10^9 /L and less than 1.0×10^9 /L). Return to chronic phase (RCP) =disappearance of features defining accelerated or blast phases but still in chronic phase.

The CHR and OHR rates were based on a minimum follow-up of 12 months for patients with AP CML and 18 months for patients with BP CML. Of the 69 evaluable patients with AP CML, 4 patients had confirmed disease transformation to BP while on BOSULIF treatment.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

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. BOSULIF (bosutinib) tablets are available in the following packaging configurations (Table 7):

Table 7:
Tablet Presentations

BOSULIF Tablets			
Package Configuration	**Tablet Strength (mg)**	**NDC**	**Tablet Description**
120 tablets per bottle	100 mg	0069-0135-01	Yellow, oval, biconvex, film-coated tablets, debossed “Pfizer” on one side and “100” on the other.
30 tablets per bottle	500 mg	0069-0136-01	Red, oval, biconvex, film-coated tablets, debossed “Pfizer” on one side and “500” on the other.

16.2 Storage

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

16.3 Handling and Disposal

Procedures for proper disposal of anticancer drugs should be considered. Any unused product or waste material should be disposed of in accordance with local requirements, or drug take back programs.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

- **Dosing and Administration**

Instruct patients to take BOSULIF exactly as prescribed, not to change their dose or to stop taking BOSULIF unless they are told to do so by their doctor. If patients miss a dose beyond 12 hours, they should be advised to take the next scheduled dose at its regular time. A double dose should not be taken to make up for any missed dose. Advise patients to take BOSULIF with food. Patients should be advised: “Do not crush or cut tablet. Do not touch or handle crushed or broken tablets.”

- **Gastrointestinal Problems**

Advise patients that they may experience diarrhea, nausea, vomiting, abdominal pain, or blood in their stools with BOSULIF and to seek medical attention promptly for these symptoms.

- **Low Blood Cell Counts**

Advise patients of the possibility of developing low blood cell counts and to immediately report fever, any suggestion of infection, or signs or symptoms suggestive of bleeding or easy bruising.

- **Liver Problems**

Advise patients of the possibility of developing liver function abnormalities and to immediately report jaundice.

- **Fluid Retention**

Advise patients of the possibility of developing fluid retention (swelling, weight gain, or shortness of breath) and to seek medical attention promptly if these symptoms arise.

- **Renal Problems**

Advise patients of the possibility of developing renal problems and to immediately report frequent urination, polyuria or oliguria

- **Other Adverse Reactions**

Advise patients that they may experience other adverse reactions such as respiratory tract infections, rash, fatigue, loss of appetite, headache, dizziness, back pain, arthralgia, or pruritus with BOSULIF and to seek medical attention if symptoms are significant. There is a possibility of anaphylactic shock.

- **Pregnancy and Breast-feeding**

Advise patients that BOSULIF can cause fetal harm when administered to a pregnant woman. Advise women of the potential hazard to the fetus and to avoid becoming pregnant. 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. 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.

Counsel females of reproductive potential to use effective contraceptive measures to prevent pregnancy during and for at least 30 days after completing treatment with BOSULIF. Instruct patients to contact their physicians immediately if they become pregnant during treatment. Advise patients not to take BOSULIF treatment while pregnant or breastfeeding. If a patient wishes to restart breastfeeding after treatment, advise her to discuss the appropriate timing with her physician.

- **Drug Interactions**

Advise patients that BOSULIF and certain other medicines, including over the counter medications or herbal supplements (such as St. John's wort) can interact with each other and may alter the effects of BOSULIF *[see Dosage and Administration (2.5) and Drug Interactions (7)]*.

LAB-0443-3.4

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

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 all the medicines you take, including prescription medicines, over-the-counter 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®)
  - clarithromycin (Biaxin®, Prevpac®)
  - conivaptan (Vaprisol®)
  - crizotinib (Xalkori®)
  - darunavir (Prezista®)
  - digoxin (Lanoxin®)
  - diltiazem (Cardizem®, Dilacor XR®, Tiazac®)

- erythromycin (Ery-tab®)
- fluconazole (Diflucan®)
- fosamprenavir (Lexiva®)
- imatinib (Gleevec®)
- indinavir (Crixivan®)
- itraconazole (Onmel®, Sporanox®)
- ketoconazole (Nizoral®)
- nefazodone (Serzone®)
- nelfinavir (Viracept®)
- posaconazole (Noxafil®)
- ritonavir (Kaletra®, Norvir®)
- saquinavir (Invirase®, Fortovase®)
- telaprevir (Incivek®)
- telithromycin (Ketek®)
- verapamil (Calan®, Covera-HS®, Tarka®, Verelan PM®)
- voriconazole (Vfend®)

- **medicines that decrease the amount of BOSULIF in your blood stream, such as:**
  - bosentan (Tracleer®)
  - carbamazepine (Carbatrol®, Equetro®, Tegretol®)
  - efavirenz (Sustiva®)
  - etravirine (Intelence®)
  - modafinil (Provigil®)
  - nafcillin (Unipen®, Nallpen®)
  - phenobarbital (Solfoton®)
  - phenytoin (Dilantin®)
  - rifabutin (Mycobutin®)
  - rifampin (Rifamate®, Rifater®, Rifadin®)
  - St. John's wort

BOSULIF is best absorbed from your stomach into your blood stream in the presence of stomach acid. You should avoid taking BOSULIF with medicines that reduce stomach acid, such as:

- esomeprazole (Nexium®), esomeprazole strontium
- dexlansoprazole (Dexilant®)
- lansoprazole (Prevacid®)
- omeprazole (Prilosec®, Vimovo®, Zegerid®)
- pantoprazole sodium (Protonix®)
- rabeprazole (AcipHex®)

Medicines that neutralize stomach acid, such as: cimetidine (Tagamet®), famotidine (Pepcid®), ranitidine (Zantac®), aluminum hydroxide/magnesium hydroxide (Maalox®), calcium carbonate (Tums®), or calcium carbonate and magnesia (Rolaids®) may be taken up to 2 hours before or 2 hours after BOSULIF.

Know the medicines you take. Keep a list of your medicines and show it to your doctor and pharmacist when you get a new medicine.

How should I take BOSULIF?

- Take BOSULIF exactly as prescribed by your doctor.
- Do not change your dose or stop taking BOSULIF without first talking with your doctor.

- Take BOSULIF with food.
- Swallow BOSULIF tablets whole. Do not crush or cut BOSULIF tablets. Do not touch or handle crushed or broken BOSULIF tablets.
- You should avoid grapefruit, grapefruit juice, and supplements that contain grapefruit extract during treatment with BOSULIF. Grapefruit products increase the amount of BOSULIF in your body.
- Your doctor may change your dose of BOSULIF or tell you to stop taking BOSULIF depending on how you respond to treatment.
- If you miss a dose of BOSULIF, take it as soon as you remember. If you miss a dose by more than 12 hours, skip that dose and take your next dose at your regular time. Do not take two doses at the same time.
- If you take too much BOSULIF, call your doctor or go to the nearest hospital emergency room right away.

What are the possible side effects of BOSULIF?

BOSULIF may cause serious side effects, including:

- **Stomach problems.** BOSULIF may cause stomach (abdomen) pain, nausea, diarrhea, or vomiting. Tell your doctor about any stomach problems.
- **Low blood cell counts**. BOSULIF may cause low platelet counts (thrombocytopenia), low red blood cell counts (anemia) and low white blood cell counts (neutropenia). Your doctor should do blood tests to check your blood cell counts regularly during your treatment with BOSULIF. Call your doctor right away if you have unexpected bleeding or bruising, blood in your urine or stools, fever, or any signs of an infection.
- **Liver problems.** BOSULIF may cause liver problems. Your doctor should do blood tests to check your liver function regularly during your treatment with BOSULIF. Call your doctor right away if your skin or the white part of your eyes turns yellow (jaundice) or you have dark “tea color” urine.
- **Your body may hold too much fluid (fluid retention).** Fluid may build up in the lining of your lungs, the sac around your heart, or your stomach cavity. Call your doctor right away if you get any of the following symptoms during your treatment with BOSULIF:
  - shortness of breath and cough
  - chest pain
  - swelling in your hands, ankles, or feet
  - swelling all over your body
  - weight gain
- **Kidney problems.** BOSULIF may cause kidney problems. Your doctor should do tests to check your kidney function when you start treatment with BOSULIF and during your treatment. Call your doctor right away if you get any of the following symptoms during your treatment with BOSULIF:
  - you urinate more often than normal
  - you urinate less often than normal
  - you make a much larger amount of urine than normal
  - you make a much smaller amount of urine than normal

Other common side effects of BOSULIF include:

- rash
- fever

- tiredness or weakness

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 a 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.

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