BOSULIF® (bosutinib) DOSING GUIDE

Once daily, with food[1]

Three tablet strengths allow you to tailor treatment to patients' individual dosing needs

Recommended daily starting dose[1]

Newly diagnosed patients

Orange tablets are **400 mg**

Patients with resistance or intolerance to prior therapy

Red tablets are **500 mg**

Additional option for dose adjustments[1]

Yellow tablets are **100 mg**

For patients with renal or hepatic impairment, please refer to dosing adjustments on page 3.
Tablets shown are not actual size.

INDICATIONS

BOSULIF is indicated for the treatment of adult patients with

- Newly diagnosed chronic phase (CP) Ph+ chronic myelogenous leukemia (CML). This indication is approved under accelerated approval based on molecular and cytogenetic response rates. Continued approval for this indication may be contingent upon verification and confirmation of clinical benefit in an ongoing long-term follow-up trial
- Chronic, accelerated, or blast phase Ph+ CML with resistance or intolerance to prior therapy

SELECTED SAFETY INFORMATION

Contraindication: History of hypersensitivity to BOSULIF. Reactions have included anaphylaxis. Anaphylactic shock occurred in less than 0.2% of treated patients in single-agent cancer studies with BOSULIF.

Ph+=Philadelphia chromosome–positive.

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Bosulif®
bosutinib tablets
500 mg | 400 mg | 100 mg

What to consider when treating a patient with BOSULIF

This dosing guide provides you with some information about starting patients on treatment with BOSULIF and dose modifications to help manage adverse reactions that may occur during treatment.

Convenient once-daily dosing[1]

Available in 400-, 500-, and 100-mg tablets

Recommended daily starting dose		Additional option for dose adjustments
Newly diagnosed patients	Patients with resistance or intolerance to prior therapy	
		
Orange tablets are **400 mg**, taken orally once daily with food	Red tablets are **500 mg**, taken orally once daily with food	Yellow tablets are **100 mg**, taken orally once daily with food

For patients with renal or hepatic impairment, please refer to dosing adjustments on page 3.
Tablets shown are not actual size.

Dosing and administration[1]

- The recommended dose is taken orally, once daily with food
- The tablet is to be swallowed whole and should not be crushed, broken, or cut
- Crushed or broken tablets should not be handled
- Continue treatment with BOSULIF until disease progression or intolerance to therapy
- If a dose is missed beyond 12 hours, the patient should skip the dose and take the usual prescribed dose on the following day

Dose escalation[1]

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

SELECTED SAFETY INFORMATION

Gastrointestinal Toxicity: Diarrhea, nausea, vomiting, and abdominal pain occur with BOSULIF. In the study of patients with newly diagnosed CP Ph+ CML, the median time to onset for diarrhea (all grades) was 3 days and the median duration per event was 3 days. In the study of patients with CML who were resistant or intolerant to prior therapy, median time to onset of diarrhea (all grades) was 2 days, median duration was 2 days, and the median number of episodes per patient was 3 (range 1-268). Monitor and manage patients using standards of care, including antidiarrheals, antiemetics, and/or fluid replacement. Withhold, dose reduce, or discontinue BOSULIF as necessary.

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BOSULIF starting dose for renal or hepatic impairment

Dose adjustments for renal or hepatic impairment[1]

The recommended starting doses for patients with renal and hepatic impairment are described below.

Dose adjustments for renal and hepatic impairment

	Recommended starting dosage	
	Newly diagnosed CP Ph+ CML	**CP, AP, or BP Ph+ CML with resistance or intolerance to prior therapy**
Normal renal and hepatic function	400 mg daily	500 mg daily
Renal impairment		
Creatinine clearance 30 to 50 mL/min	300 mg daily	400 mg daily
Creatinine clearance <30 mL/min	200 mg daily	300 mg daily
Hepatic impairment		
Mild (Child-Pugh A), moderate (Child-Pugh B), or severe (Child-Pugh C)	200 mg daily[a]	200 mg daily[a]

[a]There are no clinical data for efficacy at the dose of 200 mg once daily in patients with CML.
AP=accelerated phase; BP=blast phase; CP=chronic phase.

SELECTED SAFETY INFORMATION

Myelosuppression: Thrombocytopenia, anemia, and neutropenia occur with BOSULIF. Perform complete blood counts weekly for the first month and then monthly thereafter, or as clinically indicated. Withhold, dose reduce, or discontinue BOSULIF as necessary.

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Dose adjustments for managing toxicities[1]

The recommended dose adjustments for patients with nonhematologic adverse reactions are described below.

Dose adjustments for nonhematologic adverse reactions

Adverse reaction	Dose adjustment
Elevated liver transaminases	If elevations in liver transaminases >5 × institutional ULN occur, withhold BOSULIF until recovery to ≤2.5 × ULN and resume at 400 mg once daily thereafter. If recovery takes longer than 4 weeks, discontinue BOSULIF. If transaminase elevations ≥3 × ULN occur concurrently with bilirubin elevations >2 × ULN and alkaline phosphatase <2 × ULN (Hy's law case definition), discontinue BOSULIF.
Diarrhea	For NCI CTCAE Grade 3/4 diarrhea (increase of ≥7 stools/day over baseline/pretreatment), withhold BOSULIF until recovery to Grade ≤1. BOSULIF may be resumed at 400 mg once daily.
Other clinically significant, moderate, or severe nonhematologic toxicity	Withhold BOSULIF until the toxicity has resolved, then consider resuming BOSULIF at a dose reduced by 100 mg taken once daily. If clinically appropriate, consider re-escalating the dose of BOSULIF to the starting dose taken once daily. Doses <300 mg/day have been used in patients; however, efficacy has not been established.

NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; ULN=upper limit of normal.

SELECTED SAFETY INFORMATION

Hepatic Toxicity: BOSULIF may cause elevations in serum transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]). In a study of BOSULIF in combination with letrozole, one drug-induced liver injury occurred without alternative causes. In the study of patients with newly diagnosed CP Ph+ CML, the incidence of ALT/AST elevations was 31% and 23%, respectively. In patients with CML who were resistant or intolerant to prior therapy, the incidence of ALT/AST elevations was 18% and 15%, respectively. Twenty percent of the patients resistant or intolerant to prior therapy experienced an increase in either ALT or AST. Perform hepatic enzyme tests at least monthly for the first 3 months and as clinically indicated. In patients with transaminase elevations, monitor liver enzymes more frequently. Withhold, dose reduce, or discontinue BOSULIF as necessary. In patients with mild, moderate, or severe hepatic impairment, the recommended starting dose is 200 mg daily.

Cardiac Failure: Cardiac failure and left ventricular dysfunction have been reported in patients taking BOSULIF. These events occurred more frequently in previously treated patients than in patients with newly diagnosed CML and were more frequent in patients with advanced age or risk factors, including previous medical history of cardiac failure. In a randomized study with newly diagnosed CML, cardiac failure occurred in 1.5% of patients treated with BOSULIF compared to 0.8% of patients treated with imatinib. In a single-arm study in patients with CML who were resistant or intolerant to prior therapy, cardiac failure was observed in 5.3% of patients treated with BOSULIF. Monitor patients for signs and symptoms consistent with cardiac failure and treat as clinically indicated. Interrupt, dose reduce, or discontinue BOSULIF as necessary.

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Dose adjustments for myelosuppression[1]

Dose reductions for severe or persistent neutropenia and thrombocytopenia are described below.

Dose adjustments for neutropenia and thrombocytopenia[1]	
ANC <1000 × 10^6/L or Platelets <50,000 × 10^6/L	Withhold BOSULIF until ANC ≥1000 × 10^6/L and platelets ≥50,000 × 10^6/L.
	Resume treatment with BOSULIF at the same dose if recovery occurs within 2 weeks. If blood counts remain low for >2 weeks, upon recovery, reduce dose by 100 mg and resume treatment.
	If cytopenia recurs, reduce dose by an additional 100 mg upon recovery and resume treatment.
	Doses <300 mg/day have been used in patients; however, efficacy has not been established.

ANC=absolute neutrophil count.

Fluid retention[1]

Fluid retention occurs with BOSULIF and may manifest as pericardial effusion, pleural effusion, pulmonary edema, and/or peripheral edema. Monitor and manage patients using standards of care. Interrupt, dose reduce, or discontinue BOSULIF as necessary.

SELECTED SAFETY INFORMATION

Fluid Retention: Fluid retention occurs with BOSULIF and may cause pericardial effusion, pleural effusion, pulmonary edema, and/or peripheral edema. Monitor and manage patients using standards of care. Interrupt, dose reduce, or discontinue BOSULIF as necessary.

Renal Toxicity: An on-treatment decline in estimated glomerular filtration rate has occurred in patients treated with BOSULIF. Monitor renal function at baseline and during therapy, with particular attention to patients with preexisting renal impairment or risk factors for renal dysfunction. Lower starting doses are recommended for patients with renal impairment. For patients who have declining renal function while on BOSULIF or who cannot tolerate the starting dose, follow dose adjustment recommendations for toxicity.

Embryofetal Toxicity: BOSULIF can cause fetal harm. Women of childbearing potential should be advised of the potential hazard to the fetus and to use effective contraceptive measures while on treatment and for at least 2 weeks after the final dose.

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Gastrointestinal toxicity while taking BOSULIF® (bosutinib)[1]

70% of newly diagnosed patients experienced diarrhea
- 8% experienced Grade 3/4 diarrhea

85% of CP CML patients with resistance or intolerance to prior therapy experienced diarrhea
- 9% experienced Grade 3/4 diarrhea

76% of AP CML patients with resistance or intolerance to prior therapy experienced diarrhea
- 4% experienced Grade 3/4 diarrhea

Diarrhea experienced by newly diagnosed patients[2]

3 days	3 days	1% of patients
Median time to onset (range 1-505)	Median duration of diarrhea (range 1-436)	Discontinued due to diarrhea (n=2)

Diarrhea experienced by patients with resistance or intolerance to prior therapy[2]

2 days	2 days	1% of patients
Median time to onset (range 1-1330)	Median duration of diarrhea (range 1-2174)	Discontinued due to diarrhea (n=6)

How to help manage gastrointestinal toxicities[1]

To manage gastrointestinal toxicity, withhold, dose reduce, or discontinue BOSULIF as necessary. Monitor and manage patients using standards of care, including antidiarrheals, antiemetics, and fluid replacement. For NCI CTCAE Grade 3/4 diarrhea (increase of ≥7 stools/day over baseline/pretreatment), withhold BOSULIF until recovery to Grade ≤1. BOSULIF may be resumed at 400 mg once daily.

SELECTED SAFETY INFORMATION

Adverse Reactions: The most common adverse reactions observed in greater than or equal to 20% of patients with newly diagnosed CML were diarrhea, nausea, thrombocytopenia, rash, increased ALT, abdominal pain, and increased AST. The most common Grade 3/4 adverse reactions and laboratory abnormalities observed in greater than 10% of newly diagnosed CML patients were increased ALT and thrombocytopenia. The most common adverse reactions observed in greater than or equal to 20% of patients with CML who were resistant or intolerant to prior therapy were diarrhea, nausea, abdominal pain, rash, thrombocytopenia, vomiting, anemia, fatigue, pyrexia, cough, headache, increased ALT, and edema. The most common Grade 3/4 adverse reactions and laboratory abnormalities observed in greater than 10% of patients who were resistant or intolerant to prior therapy were thrombocytopenia, neutropenia, and anemia.

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Drug interactions[1]

- **Strong or Moderate CYP3A Inhibitors:** Concomitant use with a strong or moderate CYP3A inhibitor increased bosutinib C_{max} and AUC compared to BOSULIF alone, which may increase the risk of toxicities. Avoid the concomitant use of strong or moderate CYP3A inhibitors with BOSULIF
- **Strong CYP3A Inducers:** Concomitant use with a strong CYP3A inducer decreased bosutinib C_{max} and AUC compared to BOSULIF alone, which may reduce BOSULIF efficacy. Avoid the concomitant use of strong CYP3A inducers with BOSULIF
- **Proton Pump Inhibitors (PPIs):** Concomitant use with a PPI decreased bosutinib C_{max} and AUC compared to BOSULIF alone, which may reduce BOSULIF efficacy. As an alternative to PPIs, use short-acting antacids or H2 blockers, and separate dosing by more than 2 hours from BOSULIF dosing

AUC=area under the curve.

Examples of CYP3A inhibitors and inducers[3]

CYP3A Inhibitors	**Strong**	boceprevir, cobicistat, conivaptan, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, voriconazole
	Moderate	aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil
CYP3A Inducers	**Strong**	carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St John's wort

This table provides examples and is not intended to be an exhaustive list.

SELECTED SAFETY INFORMATION

CYP3A Inhibitors and Inducers: Avoid concurrent use with strong or moderate CYP3A inhibitors or strong CYP3A inducers.

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

Lactation: Because of the potential for serious adverse reactions in a nursing child, breastfeeding is not recommended during treatment with BOSULIF and for at least 2 weeks after the last dose.

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References: 1. BOSULIF Prescribing Information. New York, NY: Pfizer Inc. **2.** Data on file. Pfizer Inc., New York, NY. **3.** Drug development and drug interactions: table of substrates, inhibitors and inducers. U.S. Food & Drug Administration website. https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm. Updated November 14, 2017. Accessed October 31, 2019.