Bosulif®
bosutinib tablets

Indicated in newly diagnosed adults with CP Ph+ CML

Facing newly diagnosed CP Ph+ CML with BOSULIF

Dosing and safety profile considerations

BOSULIF (bosutinib) is indicated for:[1]

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

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

BOSULIF (bosutinib) is indicated for:[1]

the treatment of chronic, accelerated, or blast phase Philadelphia chromosome-positive chronic myelogenous leukemia (Ph+ CML) in adult patients with resistance or intolerance to prior tyrosine kinase inhibitor (TKI) therapy.

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

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

Most common adverse reactions for BOSULIF vs. imatinib

All grades of adverse reactions reported in >20% of patients in Phase 3 safety population

	BOSULIF 400 mg n=268 (%)	Imatinib 400 mg n=265 (%)
Diarrhea	70	34
Nausea	35	38
Thrombocytopenia, including platelet count decreased	35	20
ALT increased	31	6
Rash*	26	18
Abdominal pain†	25	15
AST increased	23	6
Neutropenia‡	11	21

Adapted from the Product Monograph.

Grade 3/4 adverse reactions reported in >5% of patients in Phase 3 safety population

	BOSULIF 400 mg n=268 (%)	Imatinib 400 mg n=265 (%)
ALT increased	19	2
Thrombocytopenia, including platelet count decreased	14	6
AST increased	10	2
Lipase increased§	10	5
Diarrhea	8	<1
Neutropenia‡	7	12
Anemia¶	3	5

Adapted from the Product Monograph.

ALT: alanine transaminase; AST: aspartate transaminase.
* Rash includes the following preferred terms: rash, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic.
† Abdominal pain includes the following preferred terms: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, gastrointestinal pain.
‡ Neutropenia includes the following preferred terms: neutropenia, neutrophil count decreased.
§ Lipase increased includes the following preferred terms: hyperlipasemia, lipase increased.
¶ Anemia includes the following preferred terms: anemia, hemoglobin decreased.

Additional safety information

Reported diarrhea events with BOSULIF

- 70% of patients reported diarrhea
- 8% reported severe Grade 3/4 diarrhea
- 1.1% reported SAEs of diarrhea
- 3 days median time to onset (all grades)
- 3 days median duration per event

Patients with these events should be managed using standard-of-care treatment, including antidiarrheal medication, and/or fluid replacement. Since some antiemetics and antidiarrheals are associated with a risk of increased QT interval prolongation with the potential to induce torsade de pointes, concomitant treatment with these agents should be carefully considered.

Rates of fluid retention

Pleural effusion:

- 2% of patients in both BOSULIF and imatinib groups
- None were Grade 3/4 in both groups

Pericardial effusion:

- 1 patient (0.4%) in the BOSULIF group experienced severe fluid retention of Grade 3 pericardial effusion

Patients should be weighed regularly, monitored for signs and symptoms of fluid retention, and managed using standard-of-care treatment, such as diuretics.

SAEs: severe adverse events.

Additional safety information (cont.)

Incidence of cardiovascular events

QTcF interval of greater than 500 msec occurred in:

- 1 BOSULIF patient
- 0 imatinib patients

Cardiac events occurred in:

- 5.2% BOSULIF—0.7% Grade 3/4
- 5.3% imatinib—1.1% Grade 3/4

Most commonly reported cardiovascular events* were:

- 1.5% electrocardiogram QT prolonged
- 1.1% atrial fibrillation
- 1.5% sinus bradycardia

Grade 3/4 reported cardiovascular events:

- 0.4% events in each of the following individual adverse events: angina, atrial fibrillation, supraventricular tachycardia, coronary artery disease, coronary artery occlusion, acute coronary syndrome, and pericardial effusion.

Monitoring for an effect on the QTc interval is advisable, and a baseline ECG is recommended prior to initiating therapy with BOSULIF and as clinically indicated. Hypokalemia or hypomagnesemia must be corrected prior to BOSULIF administration and should be monitored periodically during therapy.

ECG: electrocardiogram; QTcF: QT interval corrected by the Fridericia method.
* In clinical studies, patients with uncontrolled or significant cardiovascular disease (e.g. recent myocardial infarction, congestive heart failure, or unstable angina) were excluded.

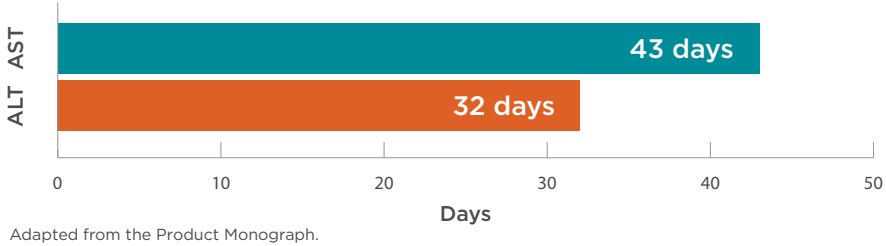
Transaminase elevations with BOSULIF

In the Phase 3 clinical trial, the incidence of transaminase elevation was:

- 31% ALT
- 23% AST

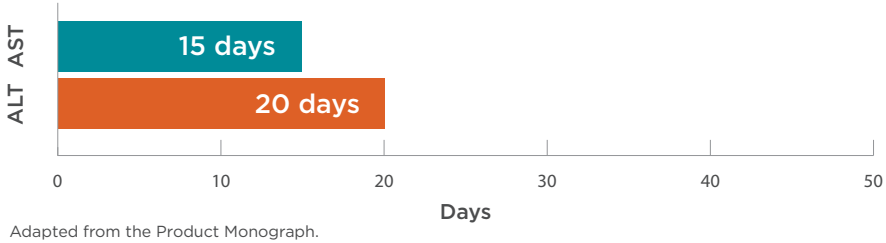
Most cases of transaminase elevation occurred early in treatment, with **79% of patients experiencing increased transaminase levels within the first 3 months**.

Median time of onset of BOSULIF transaminase elevation



Adapted from the Product Monograph.

Median duration of BOSULIF transaminase elevation



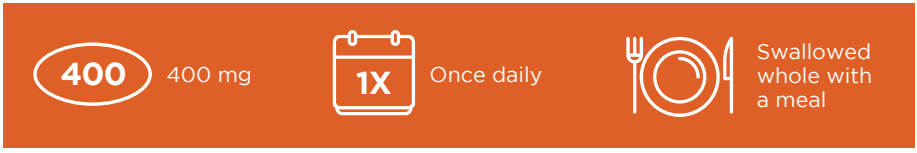
Adapted from the Product Monograph.

Patients receiving BOSULIF should have monthly hepatic enzyme tests for the first 3 months of treatment, or as clinically indicated.

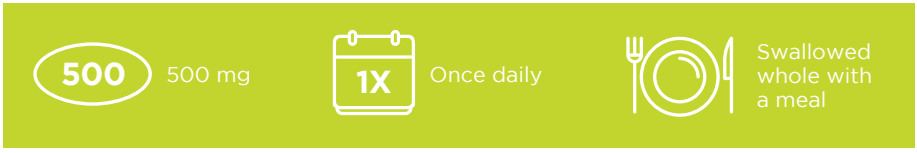
BOSULIF's convenient once-daily dosing schedule

Recommended starting dose

In newly diagnosed CP CML



In CP, AP, or BP CML with resistance or intolerance to prior therapy



Other considerations

- **In clinical trials, treatment with BOSULIF continued until disease progression or until intolerance to therapy.**
- Patients should take their dose of BOSULIF at approximately the same time each day. If a patient misses a dose (delayed by more than 12 hours), the patient should not take a dose that day but take the usual prescribed dose on the following day.
- Do not take with grapefruit products, star fruit, pomegranate, Seville oranges, and other similar fruits that are known to inhibit CYP3A4.
- Avoid concomitant use of strong or moderate CYP3A4 inhibitors or inducers with BOSULIF.
- Use caution when administering BOSULIF concomitantly with proton pump inhibitors (PPIs). Short-acting antacids should be considered as an alternative to PPIs. Administration times of BOSULIF and antacids should be separated whenever possible (e.g. take BOSULIF in the morning and antacids in the evening).
- 500 Tablets should not be crushed, cut, or dissolved in a liquid.

AP: accelerated phase; BP: blast phase.

Dose adjustments

Dose escalation

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

Dose escalations are expected to result in greater toxicity.

Dose adjustments for non-hematologic adverse reactions

Elevated liver transaminases

AST and ALT elevations	Dose adjustments
>5 x ULN	Interrupt BOSULIF until recovery to ≤2.5 x ULN. BOSULIF may be resumed at 400 mg once daily. If recovery takes >4 weeks, discontinuation of BOSULIF should be considered.
≥3 ULN	Discontinue BOSULIF if concurrent with bilirubin elevations >2 x ULN and alkaline phosphatase <2 x ULN.

ULN: upper limit of normal.

Dose adjustments (cont.)

Dose adjustments for non-hematologic adverse reactions (cont.)

Diarrhea

Grades	Dose adjustment
3/4* **Corresponding to an increase of ≥7 stools/day over baseline/ pretreatment**	Interrupt BOSULIF temporarily. Manage with standard-of-care treatment: • Antidiarrheal medication and/or • Fluid replacement BOSULIF may be resumed upon recovery to Grade ≤1 at a dose reduced by 100 mg once daily.

Other

	Dose adjustment
Clinically significant moderate or severe non-hematological toxicity	Interrupt BOSULIF until toxicity resolves. BOSULIF may be resumed at a dose reduced by 100 mg once daily. If clinically appropriate, re-escalation of the dose to the starting dose once daily may be considered. 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.
* NCI CTCAE.

Dose adjustments for hematologic adverse reactions

Neutropenia and thrombocytopenia

	Dose adjustment
ANC <1.0 x 10^9/L **or** **platelets <50 x 10^9/L**	1. Withhold BOSULIF until ANC ≥1.0 x 10^9/L and platelets ≥50 x 10^9/L. 2. 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. 3. If either 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.

Consult the Product Monograph for complete dosing information.

ANC: absolute neutrophil count.

PATIENT SUPPORT PROGRAM

Pfizer Liaison
PATIENT SUPPORT PROGRAM

Connecting patients to resources that support their treatment and complement the care provided by their healthcare team.

ACCESS TO TREATMENTS	PHARMACY SERVICES	HELPFUL RESOURCES
• Reimbursement navigation and assessment • Coordination of insurance benefits • Financial assistance	• Access to specialty pharmacies • Patient counselling • Refill reminders • Medication home delivery	• Treatment information • Referral to services and programs offered by patient groups

TO ENROL YOUR PATIENTS, OR LEARN MORE ABOUT PFIZER LIAISON, CONTACT US:

Pfizer Liaison Patient Support Program
Phone: 1-844-616-6888
Fax: 1-844-636-6888
Email: pfizerliaison@bayshore.ca

Program administered by Bayshore HealthCare Ltd. Financial assistance cannot be guaranteed.

BOSULIF safety information

Clinical use:

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

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

Contraindications:

- Patients with a known history of long QT syndrome or with a persistent QT interval of >480 ms.
- Cases of uncorrected hypokalemia or hypomagnesemia.
- Hepatically impaired patients. Higher risk of QT prolongation has been seen in patients with declining hepatic function.

Most serious warnings and precautions:

Drug interactions with inhibitors or inducers of CYP3A4. Avoid the concomitant use of strong or moderate CYP3A4 inhibitors.

Gastrointestinal toxicity, including diarrhea. Patients with recent or ongoing clinically significant gastrointestinal disorder should use BOSULIF with caution and only after a careful benefit-risk assessment.

Hepatic toxicity, including Hy's Law case. Patients receiving BOSULIF should have monthly hepatic enzyme tests for the first three months of treatment, or as clinically indicated. Patients with transaminase elevations can be managed by withholding BOSULIF temporarily, dose reduction, and/or discontinuation of BOSULIF.

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

Fluid retention, including pleural effusion, pulmonary edema, and pericardial effusion. Patients should be weighed regularly and monitored for signs and symptoms of fluid retention, and managed using standard-of-care treatment, such as diuretics. In addition, these events can also be managed by withholding BOSULIF temporarily, dose reduction, and/or discontinuation of BOSULIF.

Hemorrhage: Patients with coagulation dysfunction/low platelet counts should be closely monitored during treatment with BOSULIF.

QT interval prolongation: Should be administered with caution to patients who have a history of predisposition for QTc prolongation; who have uncontrolled or significant cardiac disease, including recent myocardial infarction, congestive heart failure, unstable angina, or clinically significant bradycardia; or who are taking medicinal products that are known to prolong the QT interval. Monitoring for an effect on the QTc interval is advisable, and a baseline ECG is recommended prior to initiating therapy with BOSULIF and as clinically indicated. Hypokalemia or hypomagnesemia must be corrected prior to BOSULIF administration and should be monitored periodically during therapy.

Other relevant warnings and precautions:

- Carcinogenesis and mutagenesis
- Preexisting cardiovascular disease
- Myelosuppression
- Elevated serum lipase and amylase
- Previous history of pancreatitis
- BOSULIF may predispose patients who are immunocompromised or older to infections
- Patients with immunocompromising disease or risk factors for immunosuppression
- Hepatitis B virus reactivation
- Potential to impair reproductive function and fertility
- Tumour lysis syndrome
- Changes in bone density. Patients with endocrine abnormalities and severe osteoporosis could be at greater risk
- Renal and urinary adverse events
- Preexisting renal compromised patients
- Respiratory disorders
- Skin: Stevens-Johnson syndrome
- Pregnant women
- Nursing women
- Female patients of childbearing potential must use highly effective contraception during treatment and for at least 1 month after the final dose
- Male patients should use highly effective contraception (including condom) during any sexual contact with females of childbearing potential even if they have undergone a successful vasectomy. The method of contraception should be used while the patient is taking BOSULIF, during interruption of treatment, and for at least 4 weeks after stopping BOSULIF
- Geriatrics: the overall frequency of adverse events leading to discontinuation was higher in older subjects
- Hypertension
- Coagulation dysfunction and platelet disorders
- Monitoring and laboratory test on CBC, serum electrolytes (including phosphorus), calcium, and magnesium

For more information:

Please consult the Product Monograph at https://www.pfizer.ca/pm/en/Bosulif.pdf for important information relating to adverse reactions, interactions, and dosing information that has not been discussed in this piece. The Product Monograph is also available by calling us at 1-800-463-6001.

CBC: complete blood count; ECG: electrocardiogram.

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Reference:

1. BOSULIF® Product Monograph. Pfizer Canada ULC. 2019.

Pfizer Oncology

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PAAB