STARTING YOUR JOURNEY

with BOSULIF® (bosutinib)

INDICATIONS

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 are newly diagnosed or who no longer benefit from or did not tolerate other treatment.

Please see important safety information on pages 4 and 5 and a brief summary of IMPORTANT FACTS about BOSULIF on the last page.

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

HOW TO USE THIS BROCHURE

In this brochure, you will find information that will help you:

- Understand CML
- Manage your treatment and side effects
- Find resources and support

Throughout, you will notice that some terms are underlined; they are defined under "Terms to know."

WHAT IS CML?

CML is chronic myelogenous leukemia. It is a type of cancer in your blood and bone marrow.

When you have CML, irregular white blood cells (WBCs) grow uncontrollably in your bone marrow and collect in your blood. These are called leukemia cells. Over time, the leukemia cells crowd out healthy WBCs, red blood cells, and platelets.

WHAT CAUSES CML?

CML can be caused by an abnormal chromosome called the Philadelphia chromosome. If your CML is caused by this chromosome, it may also be referred to as Ph+ CML. This abnormal chromosome produces an abnormal protein called BCR-ABL. BCR-ABL causes the leukemia cells to grow and divide out of control.

HOW IS CML TREATED?

Medicines called tyrosine kinase inhibitors (TKIs) can block BCR-ABL function, slowing the growth of abnormal WBCs. For some patients, this allows their WBCs to return to normal levels.

WHY AM I TAKING BOSULIF?

BOSULIF® (bosutinib) is a treatment for:

- **PATIENTS WITH NEWLY DIAGNOSED CHRONIC PHASE (CP) Ph+ CML**
  This means you are being treated for the first time.
- **PATIENTS WHO NO LONGER BENEFIT FROM OR DID NOT TOLERATE THEIR CURRENT TREATMENT FOR THEIR Ph+ CML**
  This means your medicine no longer works to control your CML or you can no longer take your current medicine due to unmanageable side effects.

Do not take BOSULIF if you are allergic to bosutinib or any of the ingredients in BOSULIF. It is not known if BOSULIF is safe and works in children less than 18 years of age.

TELL ALL OF YOUR HEALTHCARE PROVIDERS THAT YOU ARE TAKING BOSULIF

TERMS TO KNOW

BCR-ABL: An abnormal protein that causes the bone marrow to produce leukemia cells.

Bone marrow: The soft, sponge-like tissue in the center of most bones. It makes WBCs, red blood cells, and platelets.

Tyrosine kinase inhibitors (TKIs): In CML, a TKI is used to block the activity of BCR-ABL protein (a tyrosine kinase); this slows leukemia cell growth.

Philadelphia chromosome: An abnormality in your chromosome that results in the production of BCR-ABL protein. This protein causes leukemia cells to grow uncontrollably.

Please see important safety information on pages 4 and 5 and a brief summary of IMPORTANT FACTS about BOSULIF on the last page.

BOSULIF MAY CAUSE SERIOUS SIDE EFFECTS, INCLUDING:

- **Stomach problems.** BOSULIF® (bosutinib) may cause stomach (abdomen) pain, nausea, diarrhea, vomiting, or blood in your stools. Get medical help right away for 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.** 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
- **Heart problems.** BOSULIF may cause heart problems, including heart failure and decreased blood flow to the heart, which can lead to heart attack. Get medical help right away if you get shortness of breath, weight gain, chest pain, or swelling in your hands, ankles, or feet
- **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. Get medical help 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

SIDE EFFECTS (cont'd)

- **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 or less often than normal
  - you make a much larger or smaller amount of urine than normal

The most common side effects of BOSULIF in people with CML include: diarrhea, rash, nausea, stomach (abdomen) pain, vomiting, tiredness, liver problems, respiratory tract infections (infections in nose, throat, or lungs), fever, headache, and changes in certain blood tests. Your doctor may do blood tests during treatment with BOSULIF to check for changes.

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

Your doctor may change your dose, temporarily stop, or permanently stop treatment with BOSULIF if you have certain side effects.

BOSULIF may cause fertility problems in both female and male patients. This may affect your ability to have a child. Talk to your doctor if this is a concern for you.

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. You may report side effects to FDA at 1-800-FDA-1088.

DEALING WITH DIARRHEA

Diarrhea

Most patients in the clinical studies of BOSULIF® (bosutinib) experienced diarrhea. Nine percent of patients who were newly diagnosed and 10% of patients with CP CML treated before experienced episodes of severe diarrhea.

Before starting BOSULIF, ask your doctor or healthcare professional (HCP) how to prepare for possible episodes of diarrhea.

If you have diarrhea, call your doctor or HCP. Your doctor or HCP may recommend you take medicine to treat diarrhea. Always talk to your doctor before taking any over-the-counter medicines. Your doctor or HCP may change your dose, temporarily stop, or permanently stop treatment with BOSULIF to help manage diarrhea.

Experience from the clinical studies			
	What percentage of chronic phase patients experienced diarrhea?	How soon after starting treatment did diarrhea occur?[a]	How long did episodes of diarrhea last?[b]
Newly diagnosed patients	75%	Median of 4 days	Median of 3 days
Patients who were treated before	85%	Median of 2 days[c]	Median of 2 days[c]

[a]Median length of time after starting treatment that diarrhea occurred. (The median is the "middle value" in a list of numbers. It is a kind of measurement. For example, the median number of episodes of diarrhea means that half of the patients in the study experienced more episodes of diarrhea, and half experienced fewer episodes of diarrhea.)

[b]Median length of each diarrhea episode.

[c]Includes advanced phase patients.

TERMS TO KNOW

Median: The median is the midpoint in a range of numbers, where exactly half of the numbers are below and half of the numbers are above that point.

Severe diarrhea: Severe diarrhea is 7 or more stools/bowel movements per day over baseline.

MANAGEMENT TIPS FOR POTENTIAL SIDE EFFECTS

The table below contains information about some common side effects of BOSULIF® (bosutinib) and tips that may help manage them. It's important to discuss this content with your doctor or nurse and set up a plan for managing any side effects you may have. Ask your doctor or healthcare provider (HCP) if there are over-the-counter or prescription medicines that may help you. Not all side effects are manageable. Your doctor may change your dose or tell you to stop taking BOSULIF.

DIARRHEA	✓ **Hydrate:** Drink lots of water ✘ **Don't irritate:** Eat mild foods and avoid spicy and fatty foods, raw fruit, and caffeine
NAUSEA OR VOMITING	✓ Eat smaller, more frequent meals ✓ Drink fluids in small amounts ✘ Avoid foods that are sweet, fried, or fatty
RASH	✓ Wear loose clothing ✘ Avoid soaking in long, hot baths
HEARTBURN/ INDIGESTION	✓ Sleep in a more upright position, propped up on a pillow ✓ Reduce stress ✘ Avoid large meals, coffee, and alcohol
COUGH	✓ Drink warm fluids with honey and lemon ✓ Suck on sore throat lozenges
FEVER	✓ Take medicine to control fever as recommended by your HCP
TIREDNESS OR WEAKNESS	✓ Eat well and drink plenty of fluids ✓ Take short walks or do light exercise if you feel up to it ✓ Do things that are relaxing, such as listening to music or reading
HEADACHE	✘ Limit alcohol intake

QUICK TIP: USE A JOURNAL TO TRACK HOW YOU'RE FEELING

Track how you're feeling so that, together, you and your doctor or HCP can set up a plan for managing any side effects you may have.

HOW SHOULD I TAKE BOSULIF?

BOSULIF® (bosutinib) is available in 400-mg, 500-mg, and 100-mg tablets and is taken once a day with food

Tablets not shown at actual size.

Your doctor or healthcare professional (HCP) most likely started you on a dosing schedule of taking one 400-mg tablet a day if you are newly diagnosed, or one 500-mg tablet a day if you were resistant or intolerant to prior therapy. This can vary, though, depending on your individual needs. Your doctor or HCP may adjust your dose or tell you to stop taking BOSULIF if there are issues or concerns about tolerability.

ONLY YOUR DOCTOR OR HCP CAN TELL YOU IF CHANGING YOUR DOSE IS APPROPRIATE IN MANAGING YOUR THERAPY

What is a dose adjustment?

BOSULIF is available in 400-mg, 500-mg, and 100-mg tablets to allow for dose adjustments. A dose adjustment is when your doctor or HCP changes the amount of BOSULIF you're taking in order to best tailor your therapy to your individual needs. Your doctor or HCP may change your dose of BOSULIF depending on how you are doing on treatment, as it may help manage side effects and response to treatment.

MAKE SURE TO TAKE BOSULIF AS PRESCRIBED

When you take BOSULIF...

WHAT TO DO

Take BOSULIF exactly as prescribed by your doctor

Take BOSULIF with food
- It may help to take BOSULIF with the same meal every day to make it part of your routine

Swallow BOSULIF tablets whole

- 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
- Wait at least 2 hours before or 2 hours after taking BOSULIF to take an antacid or H_2 blocker medicine

WHAT NOT TO DO

DO NOT change your dose or stop taking BOSULIF without first talking to your doctor.

DO NOT crush, break, or cut BOSULIF tablets. Do not touch or handle crushed or broken BOSULIF tablets.

DO NOT take a proton pump inhibitor (PPI) medicine without talking to your doctor or pharmacist first.

DO NOT take 2 doses at the same time. If you take too much BOSULIF, call your doctor or go to the nearest hospital emergency room right away.

DO NOT consume grapefruit, grapefruit juice, and supplements that contain grapefruit extract. Grapefruit products increase the amount of BOSULIF in your body.

TERM TO KNOW

Proton pump inhibitor: A substance used to treat certain disorders of the stomach and intestines, such as heartburn and ulcers.

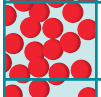
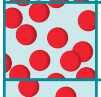
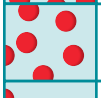
HOW DO MY DOCTOR AND I KNOW IF MY CML IS RESPONDING TO TREATMENT?

Frequent monitoring and blood tests are very important, so ask your doctor about getting tests that gauge the status of your disease and how you are responding to treatment. Monitoring with quantitative polymerase chain reaction (qPCR) every 3 months is recommended for all patients after initiating therapy, including those who meet response milestones at 3, 6, and 12 months.

In CML, qPCR measures the number of cells that have the *BCR-ABL* cancer gene.* qPCR-International Scale (IS) is how many *BCR-ABL* cells you have in your blood compared to baseline. After *BCR-ABL* 0.1%-1% has been achieved, molecular monitoring is recommended every 3 months for 2 years and every 3 to 6 months thereafter.*

Measures of response in CML	
Complete hematologic response	A return of blood cell counts to normal levels
Complete cytogenetic response (CCyR)	When there are no cells with the Philadelphia chromosome (Ph+) in your bone marrow
Molecular response	A decrease in the percentage of blood cells containing *BCR-ABL*

Below are qPCR-IS molecular response milestones that your doctor or healthcare professional will try to achieve with treatment:

qPCR milestones	
	**100% of baseline** Your *BCR-ABL* cell level before treatment
	**10% of baseline—1-log reduction**
	**1% of baseline—2-log reduction**
	**0.1% of baseline—3-log reduction**
	**0.0032% of baseline—4.5-log reduction**

Two types of responses your doctor may mention are EMR and MMR

- EMR is early molecular response, which means that at 3 and 6 months, the amount of *BCR-ABL* in your blood is ≤10% of when you started treatment
- MMR is major molecular response, which means the amount of *BCR-ABL* is ≤0.1% of what it was at baseline

*Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Myeloid Leukemia V.2.2020. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed October 23, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

WHAT ELSE SHOULD BE MONITORED DURING TREATMENT?

Your doctor may also order blood tests:

- To monitor your **blood cell counts** regularly during your treatment with BOSULIF® (bosutinib). 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
- To monitor 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

LEARN MORE ABOUT HOW BOSULIF WAS STUDIED IN CLINICAL TRIALS AT BOSULIF.COM

Please see important safety information on pages 4 and 5 and a brief summary of IMPORTANT FACTS about BOSULIF on the last page.

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bosutinib tablets
500 mg | 400 mg | 100 mg

REMINDERS TO MAKE THE MOST OF YOUR TREATMENT

Make sure to tell your doctor or healthcare professional (HCP) of any changes in:

Your medicines or any new medicines you start taking.

How you are feeling, even if you think it is not related to your CML.

Side effects, including ones that bother you or do not go away.

Your lifestyle, including any new health issues that may arise.

Start a routine

Take your medicine at the same time every day. Consider taking BOSULIF® (bosutinib) in the morning with breakfast or in the evening with dinner.

Use alarms and calendars as reminders to take medicine.

Use a pill container to organize your medicines at home and when you travel.

Your doctor or HCP can help you with side effects

When you start treatment, consider asking your doctor how to prepare for possible episodes of diarrhea, the most common side effect of BOSULIF.

Dose adjustments from your doctor, lifestyle management, and monitoring over time may help you manage side effects.

Please see important safety information on pages 4 and 5 and a brief summary of IMPORTANT FACTS about BOSULIF on the last page.

Pfizer Oncology together™

Financial Assistance

We'll help you find financial assistance options for your prescribed BOSULIF, regardless of your insurance coverage.

Eligible, commercially insured patients may pay as little as $0 per month for BOSULIF.*

We can also help identify resources if you have Medicare, another government insurance plan, or don't have health insurance.

***Limits, terms, and conditions apply.** Patients are not eligible to use this card if they are enrolled in a state or federally funded insurance program, including but not limited to Medicare, Medicaid, TRICARE, Veterans Affairs health care, a state prescription drug assistance program, or the Government Health Insurance Plan available in Puerto Rico. Patients may receive up to $25,000 in savings annually. **The offer will be accepted only at participating pharmacies. This offer is not health insurance.** No membership fees apply. Pfizer reserves the right to rescind, revoke, or amend this offer without notice. For full Terms and Conditions, please see PfizerOncologyTogether.com/terms. For any questions, please call 1-877-744-5675, visit PfizerOncologyTogether.com/terms, or write: Pfizer Oncology Together Co-Pay Savings Program, 2250 Perimeter Park Drive, Suite 300, Morrisville, NC 27560.

Personalized Support

Our Care Champions, who have social work experience, can provide you with resources that may help with some of your day-to-day challenges:

- Connections to emotional support resources
- Educational information about physical and mental health, nutrition, and BOSULIF
- Connections to independent organizations that help eligible patients find free rides and lodging for treatment-related appointments
- Information to help you prepare for leaving or returning to work

FOR LIVE, PERSONALIZED SUPPORT
Call **1-877-744-5675** (Monday-Friday 8 AM-8 PM ET)

VISIT
PfizerOncologyTogether.com

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FOR CAREGIVERS: HELPING YOUR LOVED ONE THROUGHOUT THEIR JOURNEY

When a loved one has Ph+ CML, there are many things you can do to help them through their disease and treatment. Use the information in this brochure to help them with:

- Understanding their disease and treatment
- Creating a routine with BOSULIF® (bosutinib)
- Managing potential side effects

You can make a difference in your loved one's treatment

Reminders about treatment, emotional support, and accompanying your loved one when talking to healthcare professionals (HCPs) can help make your loved one's journey with BOSULIF easier.

Use the following reminders to help your loved ones:

Review the tips for managing side effects so you know how to help them cope

Help them reach out to their doctor or HCP if they have questions or concerns

Record appointments and testing dates and remind them as they approach

Remind them to take their treatment at the same time every day

Take care of yourself while you're giving to others

There are resources available that are designed specifically for people like you, so you always feel supported.

Leukemia & Lymphoma Society® (LLS)
LLS has a Caregiver Workbook as a resource to help you support your loved ones. Call an information specialist with questions or to request a workbook.

www.LLS.org/CaregiverWorkbook | 1-800-955-4572

Caregiver Action Network
Provides education, peer support, and resources to caregivers across the United States, free of charge.

www.caregiveraction.org | 1-202-454-3970

Well Spouse Association
Advocates for and addresses the needs of individuals caring for a chronically ill and/or disabled spouse/partner.

www.wellspouse.org | 1-732-577-8899

Please see important safety information on pages 4 and 5 and a brief summary of IMPORTANT FACTS about BOSULIF on the last page.

ADDITIONAL RESOURCES TO GET YOU THE SUPPORT YOU NEED

The external programs and networks below offer additional support on your treatment journey

Leukemia & Lymphoma Society® (LLS)
An organization on the front lines of the fight to cure blood cancer. LLS is dedicated to research, patient access, and policy and advocacy. It has resources available for both patients and caregivers to help them in their journey with Ph+ CML.

www.LLS.org/CaregiverWorkbook | **1-800-955-4572**

Cancer Support Community
An international nonprofit organization dedicated to providing support, education, and hope to people affected by cancer.

www.cancersupportcommunity.org | **1-888-793-9355**

National Comprehensive Cancer Network® (NCCN®)
NCCN has materials and NCCN Guidelines for Patients®.
Go to www.nccn.org to learn more.

Learn more about CML

The following resources are available to anyone interested in additional information about CML:

American Cancer Society	**The National CML Society**	**CancerCare**
1-800-227-2345		**1-800-813-4673**
www.cancer.org	www.nationalcmlsociety.org	www.cancercare.org

Please see important safety information on pages 4 and 5 and a brief summary of IMPORTANT FACTS about BOSULIF on the last page.

IMPORTANT FACTS

WHAT IS BOSULIF (bosutinib)?

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 are newly diagnosed or who no longer benefit from or did not tolerate other treatment.

WHO SHOULD NOT TAKE BOSULIF?

Do not take BOSULIF if you are allergic to bosutinib or any of the ingredients in BOSULIF.

WHAT SHOULD I TELL MY HEALTHCARE PROVIDER BEFORE TAKING BOSULIF?

- have liver problems
- have heart problems
- have kidney problems
- have high blood pressure
- have diabetes
- are pregnant or plan to become pregnant. BOSULIF can harm your unborn baby. Tell your doctor right away if you become pregnant while taking BOSULIF
  - **Females** who are able to become pregnant should have a pregnancy test before starting treatment with BOSULIF and should use effective birth control (contraception) during treatment with BOSULIF and for at least 2 weeks after the last dose. Talk to your doctor about birth control methods that may be right for you
- are breastfeeding or plan to breastfeed. It is not known if BOSULIF passes into your breast milk or if it can harm your baby. Do not breastfeed during treatment with BOSULIF and for at least 2 weeks after the last dose

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

These consumer important facts are based on BOSULIF patient information LAB-0639-11.0, May 2021.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF BOSULIF?

- **Stomach problems.** BOSULIF may cause stomach (abdomen) pain, nausea, diarrhea, vomiting, or blood in your stools. Get medical help right away for 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.** 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
- **Heart problems.** BOSULIF may cause heart problems, including heart failure and decreased blood flow to the heart, which can lead to heart attack. Get medical help right away if you get shortness of breath, weight gain, chest pain, or swelling in your hands, ankles, or feet
- **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. Get medical help 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.** 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 or less often than normal
  - you make a much larger or smaller amount of urine than normal

The most common side effects of BOSULIF in people with CML include diarrhea, rash, nausea, stomach (abdomen) pain, vomiting, tiredness, liver problems, respiratory tract infections (infections in nose, throat, or lungs), fever, headache, and changes in certain blood tests. Your doctor may do blood tests during treatment with BOSULIF to check for changes.

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

Your doctor may change your dose, temporarily stop, or permanently stop treatment with BOSULIF if you have certain side effects.

BOSULIF may cause fertility problems in both female and male patients. This may affect your ability to have a child. Talk to your doctor if this is a concern for you.

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.

You may report side effects to FDA at 1-800-FDA-1088.

BOSULIF® (bosutinib) tablets for oral use

Initial U.S. Approval: 2012

Brief Summary of Prescribing Information

INDICATIONS AND USAGE

BOSULIF® (bosutinib) is indicated for the treatment of adult patients with newly diagnosed chronic phase (CP) Philadelphia chromosome–positive chronic myelogenous leukemia (Ph+ CML). BOSULIF is also indicated for the treatment of adult patients with CP, accelerated phase (AP), or blast phase (BP) Ph+ CML with resistance or intolerance to prior therapy.

CONTRAINDICATIONS

BOSULIF is contraindicated in patients with a history of hypersensitivity to BOSULIF. Reactions have included anaphylaxis.

WARNINGS AND PRECAUTIONS

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 randomized clinical trial in patients with newly diagnosed Ph+ CML, the median time to onset for diarrhea (all grades) was 4 days and the median duration per event was 3 days. Among 546 patients in a single-arm study in patients with CML who were resistant or intolerant to prior therapy, the median time to onset for diarrhea (all grades) was 2 days and the median duration per event was 2 days. Among the patients who experienced diarrhea, the median number of episodes of diarrhea per patient during treatment with BOSULIF was 3 (range 1-268). To manage gastrointestinal toxicity, withhold, dose reduce, or discontinue BOSULIF as necessary.

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.

Hepatic Toxicity: BOSULIF may cause elevations in serum transaminases (alanine aminotransferase [ALT], aspartate aminotransferase [AST]). Two cases consistent with drug-induced liver injury (defined as concurrent elevations in ALT or AST ≥3 x the upper limit of normal (ULN) with total bilirubin >2 x ULN and alkaline phosphatase <2 x ULN) have occurred without alternative causes. This represented 2 out of 1711 patients in BOSULIF clinical trials. In the 268 patients from the safety population in the randomized clinical trial in patients with newly diagnosed CML in the BOSULIF treatment group, the incidence of ALT elevation was 68% and AST elevation was 56%. Of patients who experienced transaminase elevations of any grade, 73% experienced their first event within the first 3 months. The median time to onset of increased ALT and AST was 29 and 56 days, respectively, and the median duration was 19 and 15 days, respectively. Among the 546 patients in a single-arm study in patients with CML who were resistant or intolerant to prior therapy, the incidence of ALT elevation was 53% and AST elevation was 47%. Sixty percent of the patients experienced an increase in either ALT or AST. Most cases of transaminase elevations in this study occurred early in treatment; of patients who experienced transaminase elevations of any grade, more than 81% experienced their first event within the first 3 months. The median time to onset of increased ALT and AST was 22 and 29 days, respectively, and the median duration for each was 21 days. Perform hepatic enzyme tests monthly for the first 3 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.

Cardiovascular Toxicity: BOSULIF can cause cardiovascular toxicity, including cardiac failure, left ventricular dysfunction, and cardiac ischemic events. Cardiac failure 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. Cardiac ischemic events occurred in both previously treated patients and in patients with newly diagnosed CML and were more common in patients with coronary artery disease risk factors, including history of diabetes, body mass index greater than 30, hypertension, and vascular disorders. In a randomized study with newly diagnosed CML, cardiac failure occurred in 1.9% of patients treated with BOSULIF compared to 0.8% of patients treated with imatinib. Cardiac ischemic events occurred in 4.9% 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 and cardiac ischemic events were observed in 4.9% of patients treated with BOSULIF. Monitor patients for signs and symptoms consistent with cardiac failure and cardiac ischemia and treat as clinically indicated. Interrupt, dose reduce, or discontinue BOSULIF as necessary.

Fluid Retention: Fluid retention occurs with BOSULIF and may manifest as pericardial effusion, pleural effusion, pulmonary edema, and/or peripheral edema. In the randomized clinical trial of 268 patients with newly diagnosed CML in the BOSULIF treatment group, 3 patients (1.1%) experienced severe fluid retention of Grade 3, 1 patient experienced Grade 3 pericardial effusion, and 2 patients experienced Grade 3 pleural effusion. Among 546 patients in a single-arm study in patients with Ph+ CML who were resistant or intolerant to prior therapy, Grade 3 or 4 fluid retention was reported in 30 patients (6%). Some patients experienced more than one fluid retention event. Specifically, 24 patients experienced Grade 3 or 4 pleural effusions, 9 patients experienced Grade 3 or Grade 4 pericardial effusions, and 6 patients experienced Grade 3 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 (eGFR) has occurred in patients treated with BOSULIF. The following table identifies the shift from baseline to lowest observed eGFR during BOSULIF therapy for patients in the pooled leukemia studies, regardless of line of therapy. The median duration of therapy with BOSULIF was approximately 24 months (range, 0.03 to 155) for patients in these studies.

Shift From Baseline to Lowest Observed eGFR Group During Treatment Safety Population in Clinical Studies (N=1372)*

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	527	115 (21.8)	330 (62.6)	50 (9.5)	23 (4.4)	3 (0.6)	5 (0.9)
Mild	672	10 (1.5)	259 (38.5)	271 (40.3)	96 (14.3)	26 (3.9)	6 (0.9)
Mild to Moderate	137	0	6 (4.4)	40 (29.2)	66 (48.2)	24 (17.5)	1 (0.7)
Moderate to Severe	33	0	1 (3.0)	1 (3.0)	8 (24.2)	19 (57.6)	4 (12.1)
Severe	1	0	0	0	0	0	1 (100)
Total	1370	125 (9.1)	596 (43.5)	362 (26.4)	193 (14.1)	72 (5.2)	17 (1.2)

Notes: eGFR was calculated using Modification in Diet in Renal Disease method (MDRD). Grading is based on Kidney Disease Improving Global Outcomes (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 1372 patients, eGFR was missing in 7 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.

Embryo-Fetal Toxicity: Based on findings from animal studies and its mechanism of action, BOSULIF can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies conducted in rats and rabbits, oral administration of bosutinib during organogenesis caused adverse developmental outcomes, including structural abnormalities, embryo-fetal mortality, and alterations to growth at maternal exposures (AUC) as low as 1.2 times the human exposure at the dose of 500 mg/day. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for at least 2 weeks after the last dose.

ADVERSE REACTIONS

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. The most common adverse reactions in ≥20% of patients with newly diagnosed CP Ph+ CML or CP, AP, or BP Ph+ CML with resistance or intolerance to prior therapy (N=814) were diarrhea (80%), rash (44%), nausea (44%), abdominal pain (43%), vomiting (33%), fatigue (33%), hepatic dysfunction (33%), respiratory tract infection (25%), pyrexia (24%), and headache (21%). The most common laboratory abnormalities that worsened from baseline in ≥20% of patients were creatinine increased (93%), hemoglobin decreased (90%), lymphocyte count decreased (72%), platelets decreased (69%), ALT increased (58%), calcium decreased (53%), white blood cell count decreased (52%), absolute neutrophil count decreased (50%), AST increased (50%), glucose increased (46%), phosphorus decreased (44%), urate increased (41%), alkaline phosphatase increased (40%), lipase increased (36%), creatine kinase increased (29%), and amylase increased (24%).

Adverse Reactions in Patients With Newly-Diagnosed CP CML: The clinical trial randomized and treated 533 patients with newly diagnosed CP CML to receive BOSULIF 400 mg daily or imatinib 400 mg daily as single agents (Newly Diagnosed CP CML Study). The safety population (received at least 1 dose of BOSULIF) included 268 patients with newly diagnosed CP CML that had a median duration of BOSULIF treatment of 55 months (range: 0.3 to 60 months) and a median dose intensity of 394 mg/day. Serious adverse reactions occurred in 22% of patients with newly diagnosed CP CML who received bosutinib. Serious adverse reactions reported in >2% of patients included hepatic dysfunction (4.1%), pneumonia (3.4%), coronary artery disease (3.4%), and gastroenteritis (2.2%). Fatal adverse reactions occurred in 3 patients (1.1%) due to coronary artery disease (0.4%), cardiac failure acute (0.4%), and renal failure (0.4%). Permanent discontinuation of bosutinib due to an adverse reaction occurred in 20% of patients with newly diagnosed CP CML who received bosutinib. Adverse reactions which resulted in permanent discontinuation in >2% of patients included hepatic dysfunction (9%). Dose modifications (dose interruption or reductions) of bosutinib due to an adverse reaction occurred in 68% of patients with newly diagnosed CP CML. Adverse reactions which required dose interruptions or reductions in >5% of patients included hepatic dysfunction (27%), thrombocytopenia (16%), diarrhea (16%), lipase increased (10%), neutropenia (7%), abdominal pain (6%), rash (5%).

The most common adverse reactions, in >20% of bosutinib-treated patients with newly diagnosed CML (N=268) were diarrhea (75%), hepatic dysfunction (45%), rash (40%), abdominal pain (39%), nausea (37%), fatigue (33%), respiratory tract infection (27%), headache (22%), and vomiting (21%). The most common laboratory abnormalities that worsened from baseline in ≥20% of patients were creatinine increased (94%), hemoglobin decreased (89%), lymphocyte count decreased (84%), ALT increased (68%), platelet count decreased (68%), glucose increased (57%), AST increased (56%), calcium decreased (55%), phosphorus decreased (54%), lipase increased (53%), white blood cell count decreased (50%), absolute neutrophil count decreased (42%), alkaline phosphatase increased (41%), creatine kinase increased (36%), and amylase increased (32%).

Adverse reactions with ≥10% incidence in patients with newly diagnosed CML who received BOSULIF 400 mg (N=268) vs imatinib 400 mg (N=265) (BOSULIF all grades [%]/Grade 3-4 [%] vs imatinib) were diarrhea (75/9 vs 40/1); hepatic dysfunction[a] (45/27 vs 15/4); rash[b] (40/2 vs 30/2); abdominal pain[c] (39/2 vs 27/1); nausea (37/0 vs 42/0); fatigue[d] (33/1 vs 30/<1); respiratory tract infection[e] (27/1 vs 25/<1); headache (22/1 vs 15/1); vomiting (21/1 vs 20/0); arthralgia (18/1 vs 18/<1); pyrexia (17/1 vs 11/0); edema[f] (15/0 vs 46/2); constipation (13/0 vs 6/0); back pain (12/<1 vs 9/<1); pruritus (11/<1 vs 4/0); cough (11/0 vs 10/0); dyspnea (11/1 vs 6/1); decreased appetite (11/<1 vs 6/0); hypertension[g] (10/5 vs 11/5).

[a]Hepatic dysfunction includes the preferred terms: Alanine aminotransferase increased, Aspartate aminotransferase, Aspartate aminotransferase increased, Bilirubin conjugated increased, Blood alkaline phosphatase increased, Blood bilirubin increased, Drug-induced liver injury, Gamma-glutamyltransferase increased, Hepatic enzyme increased, Hepatic steatosis, Hepatitis, Hepatitis toxic, Hepatocellular injury, Hepatotoxicity, Hyperbilirubinemia, Jaundice, Liver disorder, Liver function test increased, Ocular icterus, Transaminases increased.

[b]Rash includes the following preferred terms: Acne, Blister, Dermatitis, Dermatitis acneiform, Dermatitis bullous, Dermatitis exfoliative generalized, Drug reaction with eosinophilia and systemic symptoms, Dyshidrotic eczema, Eczema, Eczema asteatotic, Erythema, Erythema nodosum, Genital rash, Lichen planus, Perivascular dermatitis, Photosensitivity reaction, Psoriasis, Rash, Rash erythematous, Rash macular, Rash maculopapular, Rash papular, Rash pruritic, Rash pustular, Rash vesicular, Seborrheic keratosis, Skin discoloration, Skin exfoliation, Skin hypopigmentation, Skin irritation, Skin lesion, Stasis dermatitis.

[c]Abdominal pain includes the following preferred terms: Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness, Dyspepsia, Epigastric discomfort, Gastrointestinal pain.

[d]Fatigue includes the following preferred terms: Asthenia, Fatigue, Malaise.

[e]Respiratory tract infection includes the following preferred terms: Nasopharyngitis, Respiratory tract congestion, Respiratory tract infection, Respiratory tract infection viral, Upper respiratory tract infection.

[f]Edema includes the following preferred terms: Eye edema, Eyelid edema, Face edema, Edema, Edema peripheral, Orbital edema, Periorbital edema, Periorbital swelling, Peripheral swelling, Swelling, Swelling face, Swelling of eyelid, Swollen tongue.

[g]Hypertension includes the preferred terms: Blood pressure systolic increased, Hypertension, Hypertensive crisis, Hypertensive heart disease, Retinopathy hypertensive.

In the randomized study in patients with newly diagnosed CP CML, one patient in the group treated with BOSULIF experienced a Grade 3 QTcF prolongation (>500 msec). Patients with uncontrolled or significant cardiovascular disease, including QT interval prolongation, were excluded by protocol.

Laboratory Abnormalities ≥20% That Worsened From Baseline in Patients With Newly Diagnosed CML in the BOSULIF 400 mg Study Based on a Minimum of 57 Months of Follow-Up (bosutinib [all grades/grade 3/4] vs imatinib [all grades/grade 3/4]): Hematology parameters were platelet count decreased (68/14 vs 60/6); absolute neutrophil count decreased (42/9 vs 65/20); hemoglobin decreased (89/9 vs 90/7); white blood cell count decreased (50/6 vs 70/8); lymphocyte count decreased (84/12 vs 82/14). Biochemistry parameters were serum glutamic-pyruvic transaminase (SGPT)/ALT increased (68/26 vs 28/3); serum glutamic-oxaloacetic transaminase (SGOT)/AST increased (56/13 vs 29/3.4); lipase increased (53/19 vs 35/8); phosphorus decreased (54/9 vs 69/21); amylase increased (32/3.4 vs 18/2.3); alkaline phosphatase increased (41/0 vs 43/0.4); calcium decreased (55/1.5 vs 57/1.1); glucose increased (57/3 vs 65/3.4); creatine kinase increased (36/3 vs 65/5); creatinine increased (94/1.1 vs 98/0.8).

Adverse Reactions in Patients With Imatinib-Resistant or -Intolerant Ph+ CP, AP, and BP CML: The single-arm clinical trial enrolled patients with Ph+ CP, AP, or BP CML and with resistance or intolerance to prior therapy. The safety population (received at least 1 dose of BOSULIF) included 546 CML patients: 284 patients with CP CML previously treated with imatinib only who had a median duration of BOSULIF treatment of 26 months (range: 0.2 to 155 months), and a median dose intensity of 437 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 (range: 0.2 to 148 months) and a median dose intensity of 427 mg/day; and 143 patients with advanced phase (AdvP) CML, including 79 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 (range: 0.1 to 140 months) and 3 months (range: 0.03 to 71 months), respectively. The median dose intensity was 406 mg/day and 456 mg/day in the AP CML and BP CML cohorts, respectively. Serious adverse reactions occurred in 30% of patients in the safety population of the single-arm trial in patients with CML (N=546) who were resistant or intolerant to prior therapy. Serious adverse reactions reported in >2% of patients included pneumonia (7%), pleural effusion (6%), pyrexia (3.7%), coronary artery disease (3.5%), dyspnea (2.6%), rash (2.2%), thrombocytopenia (2%), abdominal pain (2%), and diarrhea (2%). Fatal adverse reactions occurred in 12 patients (2.2%) due to coronary artery disease (0.9%), pneumonia (0.4%), respiratory failure (0.4%), gastrointestinal hemorrhage (0.2%), acute kidney injury (0.2%), and acute pulmonary edema (0.2%).

Permanent discontinuation of bosutinib due to an adverse reaction occurred in 22% of patients with CML who were resistant or intolerant to prior therapy. Adverse reactions which resulted in permanent discontinuation in >2% of patients included thrombocytopenia (6%), hepatic dysfunction (3.3%), and neutropenia (2%). Dose modifications (dose interruption or reductions) of bosutinib due to an adverse reaction occurred in 66% of patients with CML who were resistant or intolerant to prior therapy. Adverse reactions which required dose interruptions or reductions in >5% of patients included thrombocytopenia (24%), diarrhea (14%), rash (13%), hepatic dysfunction (10%), neutropenia (9%), pleural effusion (8%), vomiting (7%), anemia (6%), and abdominal pain (6%). The most common adverse reactions, in ≥20% of patients in the safety population of the single-arm trial in patients with CML (N=546) who were resistant or intolerant to prior therapy were diarrhea (83%), nausea (47%), rash (46%), abdominal pain (45%), vomiting (39%), fatigue (33%), pyrexia (28%), hepatic dysfunction (27%), respiratory tract infection (24%), cough (23%), and headache (21%).

The most common laboratory abnormalities that worsened from baseline in ≥20% were creatinine increased (93%), hemoglobin decreased (91%), lymphocyte decreased (80%), platelets decreased (69%), absolute neutrophil count (54%), ALT increased (53%), calcium decreased (53%), white blood cell count decreased (52%), urate increased (48%), AST increased (47%), phosphorus decreased (39%), alkaline phosphatase increased (39%), lipase increased (28%), magnesium increased (25%), potassium decreased (24%), potassium increased (23%).

Adverse reactions (all grades [%]/Grade 3/4 [%]) with ≥10% incidence in patients with CP CML who were resistant or intolerant to prior therapy in the single-arm trial (N=403) based on long-term follow-up (based on a minimum of 105 months) were diarrhea (85/10), abdominal pain[a] (49/2), rash[b] (48/9), nausea (47/1), vomiting (38/3), fatigue (35/3), hepatic dysfunction[c] (29/11), respiratory tract infection[d] (27/<1), pyrexia (25/1), cough (24/0), headache (21/1), edema[e] (19/<1), arthralgia (19/1), constipation (15/<1), pleural effusion (14/4), back pain (14/1), decreased appetite (14/1), pruritus (12/1), dyspnea (12/2), influenza[f] (11/1), dizziness (11/0), hypertension[g] (11/3), pneumonia[h] (10/4).

Adverse reactions (all grades [%]/Grade 3/4 [%]) with ≥10% incidence in patients with AdvP CML who were resistant or intolerant to prior therapy in the single-arm trial (N=143) based on long-term follow-up were diarrhea (76/4), nausea (48/2), vomiting (43/3), rash[b] (42/5), pyrexia (37/3), abdominal pain[a] (36/7), fatigue (27/6), cough (22/0), hepatic dysfunction[c] (21/10), dyspnea (20/6), pneumonia[h] (18/12), headache (18/4), constipation (17/1), edema[e] (17/1), respiratory tract infection[d] (17/0), arthralgia (15/0), dizziness (14/1), decreased appetite (14/0), chest pain[i] (12/1).

[a]Abdominal pain includes the following preferred terms: Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness, Dyspepsia, Epigastric discomfort, Gastrointestinal pain, Hepatic pain.

[b]Rash includes the following preferred terms: Acarodermatitis, Acne, Angular cheilitis, Blister, Dermatitis, Dermatitis acneiform, Dermatitis psoriasiform, Drug eruption, Eczema, Eczema asteatotic, Erythema, Erythema annulare, Exfoliative rash, Lichenoid keratosis, Palmar erythema, Photosensitivity reaction, Pigmentation disorder, Psoriasis, Pyoderma gangrenosum, Pyogenic granuloma, Rash, Rash erythematous, Rash generalized, Rash macular, Rash maculopapular, Rash pruritic, Rash pustular, Seborrheic dermatitis, Seborrheic keratosis, Skin depigmentation, Skin discoloration, Skin disorder, Skin exfoliation, Skin hyperpigmentation, Skin hypopigmentation, Skin irritation, Skin lesion, Skin plaque, Skin toxicity, Stasis dermatitis.

[c]Hepatic dysfunction includes the following preferred terms: Alanine aminotransferase increased, Aspartate aminotransferase increased, Bilirubin conjugated increased, Blood alkaline phosphatase increased, Blood bilirubin increased, Blood bilirubin unconjugated increased, Gamma-glutamyltransferase increased, Hepatic enzyme increased, Hepatic function abnormal, Hepatic steatosis, Hepatitis toxic, Hepatomegaly, Hepatotoxicity, Hyperbilirubinemia, Liver disorder, Liver function test abnormal, Liver function test increased, Transaminases increased.

[d]Respiratory tract infection includes the following preferred terms: Nasopharyngitis, Respiratory tract congestion, Respiratory tract infection, Respiratory tract infection viral, Upper respiratory tract infection, Viral upper respiratory tract infection.

[e]Edema includes the following preferred terms: Eye edema, Eyelid edema, Face edema, Generalized edema, Localized edema, Edema, Edema peripheral, Penile edema, Periorbital edema, Periorbital swelling, Peripheral swelling, Scrotal edema, Scrotal swelling, Swelling, Swelling face, Swelling of eyelid, Testicular edema, Tongue edema.

[f]Influenza includes the following preferred terms: H1N1 influenza, Influenza.

[g]Hypertension* includes the following preferred terms: Blood pressure increased, Blood pressure systolic increased, Essential hypertension, Hypertension, Hypertensive crisis, Retinopathy hypertensive.

[h]Pneumonia includes the following preferred terms: Atypical pneumonia, Lower respiratory tract congestion, Lower respiratory tract infection, Pneumonia, Pneumonia aspiration, Pneumonia bacterial, Pneumonia fungal, Pneumonia necrotizing, Pneumonia streptococcal.

[i]Chest pain includes the following preferred terms: Chest discomfort, Chest pain.

*ADR identified postmarketing.

In the single-arm study in patients with CML who were resistant or intolerant to prior therapy, 2 patients (0.4%) experienced QTcF interval of greater than 500 msec. Patients with uncontrolled or significant cardiovascular disease, including QT interval prolongation, were excluded by protocol.

Number (%) of Patients with Clinically Relevant All Grade or Grade 3/4 Laboratory Test Abnormalities in the Safety Population of the Study of Patients With CML Who Were Resistant or Intolerant to Prior Therapy (CP [all grades/grade 3/4]; AdvP [all grades/grade 3/4]): Hematology parameters were platelet count decreased (66/26; 80/57), absolute neutrophil count decreased (50/16; 66/39), hemoglobin decreased (89/13; 97/38), lymphocyte decreased (79/14; 82/21), white blood cell count decreased (51/7; 57/27). Biochemistry parameters were SGPT/ALT increased (58/11; 39/6), SGOT/AST increased (50/5; 37/3.5), lipase increased (32/12; 19/6), phosphorus decreased (41/8; 33/7), total bilirubin increased (16/0.7; 22/2.8), creatinine increased (95/3; 87/1.4), alkaline phosphatase increased (39/0; 39/1.4), glucose increased (42/2.7; 39/6), sodium increased (23/0.5; 11/0), sodium decreased (18/2.2; 27/6), calcium decreased (55/4.7; 45/3.5), urate increased (49/6; 43/6), magnesium increased (27/7; 18/4.9), potassium decreased (22/1.7; 29/4.9), potassium increased (25/2.7; 19/2.1).

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 all 1372 patients with 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: *0.1% and less than 1%* - 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

Endocrine Disorders: *1% and less than 10%* - Hypothyroidism; *0.1% and less than 1%* - Hyperthyroidism

Gastrointestinal Disorders: *1% and less than 10%* - Gastritis, Pancreatitis (includes Edematous pancreatitis, Pancreatic enzymes increased, Pancreatitis, Pancreatitis acute, Pancreatitis chronic), Gastrointestinal hemorrhage (includes Anal hemorrhage, Gastric hemorrhage, Gastrointestinal hemorrhage, Intestinal hemorrhage, Lower gastrointestinal hemorrhage, Rectal hemorrhage, Upper gastrointestinal hemorrhage)

General Disorders and Administrative Site Conditions: *1% and less than 10%* - Pain

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%* - Bronchitis

Investigations: *1% and less than 10%* - Electrocardiogram QT prolonged (includes Electrocardiogram QT prolonged, Long QT syndrome)

Metabolism and Nutrition Disorders: *1% and less than 10%* - Dehydration

Musculoskeletal and Connective Tissue Disorders: *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 kidney injury, Renal impairment, Renal failure

Respiratory, Thoracic, and Mediastinal Disorders: *1% and less than 10%* - Pulmonary hypertension (includes Pulmonary hypertension, Pulmonary arterial hypertension, Pulmonary arterial pressure increased); *0.1% and less than 1%* - Acute pulmonary edema (includes Acute pulmonary edema, Pulmonary edema), Respiratory failure

Skin and Subcutaneous Disorders: *0.1% and less than 1%* - Erythema multiforme

Postmarketing Experience

The following additional adverse reactions have been identified during post-approval use of BOSULIF. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: Thrombotic microangiopathy

Skin and Subcutaneous Tissue Disorders: Stevens-Johnson syndrome

DRUG INTERACTIONS

Effect of Other Drugs on Bosulif

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 (PPI): 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.

USE IN SPECIFIC POPULATIONS

Pregnancy: Based on findings from animal studies and its mechanism of action, BOSULIF can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies conducted in rats and rabbits, oral administration of bosutinib during organogenesis caused adverse developmental outcomes, including structural abnormalities, embryo-fetal mortality, and alterations to growth at maternal exposures (AUC) as low as 1.2 times the human exposure at the dose of 500 mg/day. Advise pregnant women of the potential risk to a fetus. **Lactation:** No data are available regarding the presence of bosutinib or its metabolites in human milk or its effects on a breastfed child or on milk production. However, bosutinib is present in the milk of lactating rats. 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.

Females and Males of Reproductive Potential: Based on findings from animal studies, BOSULIF can cause fetal harm when administered to a pregnant woman. Females of reproductive potential should have a pregnancy test prior to starting treatment with BOSULIF. Advise females of reproductive potential to use effective contraception (methods that result in less than 1% pregnancy rates) during treatment with BOSULIF and for at least 2 weeks after the last dose. The risk of infertility in females or males of reproductive potential has not been studied in humans. Based on findings from animal studies, BOSULIF may cause reduced fertility in females and males of reproductive potential.

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

Geriatric Use: In the single-arm study in patients with CML who were resistant or intolerant to prior therapy of BOSULIF in patients with Ph+ CML, 20% were age 65 and over and 4% were 75 and over. Of the 268 patients who received bosutinib in the study for newly diagnosed CML, 20% were age 65 and over, 5% 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.

Renal Impairment: Reduce the BOSULIF starting dose in patients with moderate (creatinine clearance [CL_{cr}] 30 to 50 mL/min, estimated by Cockcroft-Gault [C-G]) and severe (CL_{cr} less than 30 mL/min, C-G) renal impairment at baseline. For patients who have declining renal function while on BOSULIF who cannot tolerate the starting dose, follow dose adjustment recommendations for toxicity. BOSULIF has not been studied in patients undergoing hemodialysis.

Hepatic Impairment: Reduce the BOSULIF dosage in patients with hepatic impairment (Child-Pugh A, B, or C).

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling. **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, break, 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. **Cardiovascular Problems:** Advise patients that cardiac failure, left ventricular dysfunction, and cardiac ischemic events have been reported. Advise patients to seek immediate medical attention if any symptoms suggestive of cardiac failure and cardiac ischemia occur, such as shortness of breath, weight gain, or fluid retention. **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. **Embryo-Fetal Toxicity:** Advise females to inform their healthcare provider if they are pregnant or become pregnant. Inform female patients of the risk to a fetus and potential loss of the pregnancy. Advise females of reproductive potential to use effective contraception during treatment and for at least 2 weeks after receiving the last dose of BOSULIF. Advise lactating women not to breastfeed during treatment with BOSULIF and for at least 2 weeks after the last dose. **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.

Rx only

This brief summary is based on BOSULIF Prescribing Information 0443-14.7, revised May 2021.

Pfizer Oncology

BOSULIF® (bosutinib) tablets for oral use

Initial U.S. Approval: 2012

Brief Summary of Prescribing Information

INDICATIONS AND USAGE

BOSULIF® (bosutinib) is indicated for the treatment of adult patients with newly diagnosed chronic phase (CP) Philadelphia chromosome–positive chronic myelogenous leukemia (Ph+ CML). BOSULIF is also indicated for the treatment of adult patients with CP, accelerated phase (AP), or blast phase (BP) Ph+ CML with resistance or intolerance to prior therapy.

CONTRAINDICATIONS

BOSULIF is contraindicated in patients with a history of hypersensitivity to BOSULIF. Reactions have included anaphylaxis.

WARNINGS AND PRECAUTIONS

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 randomized clinical trial in patients with newly diagnosed Ph+ CML, the median time to onset for diarrhea (all grades) was 4 days and the median duration per event was 3 days. Among 546 patients in a single-arm study in patients with CML who were resistant or intolerant to prior therapy, the median time to onset for diarrhea (all grades) was 2 days and the median duration per event was 2 days. Among the patients who experienced diarrhea, the median number of episodes of diarrhea per patient during treatment with BOSULIF was 3 (range 1-268). To manage gastrointestinal toxicity, withhold, dose reduce, or discontinue BOSULIF as necessary.

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.

Hepatic Toxicity: BOSULIF may cause elevations in serum transaminases (alanine aminotransferase [ALT], aspartate aminotransferase [AST]). Two cases consistent with drug-induced liver injury (defined as concurrent elevations in ALT or AST ≥3 x the upper limit of normal (ULN) with total bilirubin >2 x ULN and alkaline phosphatase <2 x ULN) have occurred without alternative causes. This represented 2 out of 1711 patients in BOSULIF clinical trials. In the 268 patients from the safety population in the randomized clinical trial in patients with newly diagnosed CML in the BOSULIF treatment group, the incidence of ALT elevation was 68% and AST elevation was 56%. Of patients who experienced transaminase elevations of any grade, 73% experienced their first event within the first 3 months. The median time to onset of increased ALT and AST was 29 and 56 days, respectively, and the median duration was 19 and 15 days, respectively. Among the 546 patients in a single-arm study in patients with CML who were resistant or intolerant to prior therapy, the incidence of ALT elevation was 53% and AST elevation was 47%. Sixty percent of the patients experienced an increase in either ALT or AST. Most cases of transaminase elevations in this study occurred early in treatment; of patients who experienced transaminase elevations of any grade, more than 81% experienced their first event within the first 3 months. The median time to onset of increased ALT and AST was 22 and 29 days, respectively, and the median duration for each was 21 days. Perform hepatic enzyme tests monthly for the first 3 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.

Cardiovascular Toxicity: BOSULIF can cause cardiovascular toxicity, including cardiac failure, left ventricular dysfunction, and cardiac ischemic events. Cardiac failure 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. Cardiac ischemic events occurred in both previously treated patients and in patients with newly diagnosed CML and were more common in patients with coronary artery disease risk factors, including history of diabetes, body mass index greater than 30, hypertension, and vascular disorders. In a randomized study with newly diagnosed CML, cardiac failure occurred in 1.9% of patients treated with BOSULIF compared to 0.8% of patients treated with imatinib. Cardiac ischemic events occurred in 4.9% 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 and cardiac ischemic events were observed in 4.9% of patients treated with BOSULIF. Monitor patients for signs and symptoms consistent with cardiac failure and cardiac ischemia and treat as clinically indicated. Interrupt, dose reduce, or discontinue BOSULIF as necessary.

Fluid Retention: Fluid retention occurs with BOSULIF and may manifest as pericardial effusion, pleural effusion, pulmonary edema, and/or peripheral edema. In the randomized clinical trial of 268 patients with newly diagnosed CML in the BOSULIF treatment group, 3 patients (1.1%) experienced severe fluid retention of Grade 3, 1 patient experienced Grade 3 pericardial effusion, and 2 patients experienced Grade 3 pleural effusion. Among 546 patients in a single-arm study in patients with Ph+ CML who were resistant or intolerant to prior therapy, Grade 3 or 4 fluid retention was reported in 30 patients (6%). Some patients experienced more than one fluid retention event. Specifically, 24 patients experienced Grade 3 or 4 pleural effusions, 9 patients experienced Grade 3 or Grade 4 pericardial effusions, and 6 patients experienced Grade 3 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 (eGFR) has occurred in patients treated with BOSULIF. The following table identifies the shift from baseline to lowest observed eGFR during BOSULIF therapy for patients in the pooled leukemia studies, regardless of line of therapy. The median duration of therapy with BOSULIF was approximately 24 months (range, 0.03 to 155) for patients in these studies.

Shift From Baseline to Lowest Observed eGFR Group During Treatment Safety Population in Clinical Studies (N=1372)*

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	527	115 (21.8)	330 (62.6)	50 (9.5)	23 (4.4)	3 (0.6)	5 (0.9)
Mild	672	10 (1.5)	259 (38.5)	271 (40.3)	96 (14.3)	26 (3.9)	6 (0.9)
Mild to Moderate	137	0	6 (4.4)	40 (29.2)	66 (48.2)	24 (17.5)	1 (0.7)
Moderate to Severe	33	0	1 (3.0)	1 (3.0)	8 (24.2)	19 (57.6)	4 (12.1)
Severe	1	0	0	0	0	0	1 (100)
Total	1370	125 (9.1)	596 (43.5)	362 (26.4)	193 (14.1)	72 (5.2)	17 (1.2)

Notes: eGFR was calculated using Modification in Diet in Renal Disease method (MDRD). Grading is based on Kidney Disease Improving Global Outcomes (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 1372 patients, eGFR was missing in 7 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.

Embryo-Fetal Toxicity: Based on findings from animal studies and its mechanism of action, BOSULIF can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies conducted in rats and rabbits, oral administration of bosutinib during organogenesis caused adverse developmental outcomes, including structural abnormalities, embryo-fetal mortality, and alterations to growth at maternal exposures (AUC) as low as 1.2 times the human exposure at the dose of 500 mg/day. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for at least 2 weeks after the last dose.

ADVERSE REACTIONS

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. The most common adverse reactions in ≥20% of patients with newly diagnosed CP Ph+ CML or CP, AP, or BP Ph+ CML with resistance or intolerance to prior therapy (N=814) were diarrhea (80%), rash (44%), nausea (44%), abdominal pain (43%), vomiting (33%), fatigue (33%), hepatic dysfunction (33%), respiratory tract infection (25%), pyrexia (24%), and headache (21%). The most common laboratory abnormalities that worsened from baseline in ≥20% of patients were creatinine increased (93%), hemoglobin decreased (90%), lymphocyte count decreased (72%), platelets decreased (69%), ALT increased (58%), calcium decreased (53%), white blood cell count decreased (52%), absolute neutrophil count decreased (50%), AST increased (50%), glucose increased (46%), phosphorus decreased (44%), urate increased (41%), alkaline phosphatase increased (40%), lipase increased (36%), creatine kinase increased (29%), and amylase increased (24%).

Adverse Reactions in Patients With Newly-Diagnosed CP CML: The clinical trial randomized and treated 533 patients with newly diagnosed CP CML to receive BOSULIF 400 mg daily or imatinib 400 mg daily as single agents (Newly Diagnosed CP CML Study). The safety population (received at least 1 dose of BOSULIF) included 268 patients with newly diagnosed CP CML that had a median duration of BOSULIF treatment of 55 months (range: 0.3 to 60 months) and a median dose intensity of 394 mg/day. Serious adverse reactions occurred in 22% of patients with newly diagnosed CP CML who received bosutinib. Serious adverse reactions reported in >2% of patients included hepatic dysfunction (4.1%), pneumonia (3.4%), coronary artery disease (3.4%), and gastroenteritis (2.2%). Fatal adverse reactions occurred in 3 patients (1.1%) due to coronary artery disease (0.4%), cardiac failure acute (0.4%), and renal failure (0.4%). Permanent discontinuation of bosutinib due to an adverse reaction occurred in 20% of patients with newly diagnosed CP CML who received bosutinib. Adverse reactions which resulted in permanent discontinuation in >2% of patients included hepatic dysfunction (9%). Dose modifications (dose interruption or reductions) of bosutinib due to an adverse reaction occurred in 68% of patients with newly diagnosed CP CML. Adverse reactions which required dose interruptions or reductions in >5% of patients included hepatic dysfunction (27%), thrombocytopenia (16%), diarrhea (16%), lipase increased (10%), neutropenia (7%), abdominal pain (6%), rash (5%).

The most common adverse reactions, in >20% of bosutinib-treated patients with newly diagnosed CML (N=268) were diarrhea (75%), hepatic dysfunction (45%), rash (40%), abdominal pain (39%), nausea (37%), fatigue (33%), respiratory tract infection (27%), headache (22%), and vomiting (21%). The most common laboratory abnormalities that worsened from baseline in ≥20% of patients were creatinine increased (94%), hemoglobin decreased (89%), lymphocyte count decreased (84%), ALT increased (68%), platelet count decreased (68%), glucose increased (57%), AST increased (56%), calcium decreased (55%), phosphorus decreased (54%), lipase increased (53%), white blood cell count decreased (50%), absolute neutrophil count decreased (42%), alkaline phosphatase increased (41%), creatine kinase increased (36%), and amylase increased (32%).

Adverse reactions with ≥10% incidence in patients with newly diagnosed CML who received BOSULIF 400 mg (N=268) vs imatinib 400 mg (N=265) (BOSULIF all grades [%]/Grade 3-4 [%] vs imatinib) were diarrhea (75/9 vs 40/1); hepatic dysfunction[a] (45/27 vs 15/4); rash[b] (40/2 vs 30/2); abdominal pain[c] (39/2 vs 27/1); nausea (37/0 vs 42/0); fatigue[d] (33/1 vs 30/<1); respiratory tract infection[e] (27/1 vs 25/<1); headache (22/1 vs 15/1); vomiting (21/1 vs 20/0); arthralgia (18/1 vs 18/<1); pyrexia (17/1 vs 11/0); edema[f] (15/0 vs 46/2); constipation (13/0 vs 6/0); back pain (12/<1 vs 9/<1); pruritus (11/<1 vs 4/0); cough (11/0 vs 10/0); dyspnea (11/1 vs 6/1); decreased appetite (11/<1 vs 6/0); hypertension[g] (10/5 vs 11/5).

[a]Hepatic dysfunction includes the preferred terms: Alanine aminotransferase increased, Aspartate aminotransferase, Aspartate aminotransferase increased, Bilirubin conjugated increased, Blood alkaline phosphatase increased, Blood bilirubin increased, Drug-induced liver injury, Gamma-glutamyltransferase increased, Hepatic enzyme increased, Hepatic steatosis, Hepatitis, Hepatitis toxic, Hepatocellular injury, Hepatotoxicity, Hyperbilirubinemia, Jaundice, Liver disorder, Liver function test increased, Ocular icterus, Transaminases increased.

[b]Rash includes the following preferred terms: Acne, Blister, Dermatitis, Dermatitis acneiform, Dermatitis bullous, Dermatitis exfoliative generalized, Drug reaction with eosinophilia and systemic symptoms, Dyshidrotic eczema, Eczema, Eczema asteatotic, Erythema, Erythema nodosum, Genital rash, Lichen planus, Perivascular dermatitis, Photosensitivity reaction, Psoriasis, Rash, Rash erythematous, Rash macular, Rash maculopapular, Rash papular, Rash pruritic, Rash pustular, Rash vesicular, Seborrheic keratosis, Skin discoloration, Skin exfoliation, Skin hypopigmentation, Skin irritation, Skin lesion, Stasis dermatitis.

[c]Abdominal pain includes the following preferred terms: Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness, Dyspepsia, Epigastric discomfort, Gastrointestinal pain.

[d]Fatigue includes the following preferred terms: Asthenia, Fatigue, Malaise.

[e]Respiratory tract infection includes the following preferred terms: Nasopharyngitis, Respiratory tract congestion, Respiratory tract infection, Respiratory tract infection viral, Upper respiratory tract infection.

[f]Edema includes the following preferred terms: Eye edema, Eyelid edema, Face edema, Edema, Edema peripheral, Orbital edema, Periorbital edema, Periorbital swelling, Peripheral swelling, Swelling, Swelling face, Swelling of eyelid, Swollen tongue.

[g]Hypertension includes the preferred terms: Blood pressure systolic increased, Hypertension, Hypertensive crisis, Hypertensive heart disease, Retinopathy hypertensive.

In the randomized study in patients with newly diagnosed CP CML, one patient in the group treated with BOSULIF experienced a Grade 3 QTcF prolongation (>500 msec). Patients with uncontrolled or significant cardiovascular disease, including QT interval prolongation, were excluded by protocol.

Laboratory Abnormalities ≥20% That Worsened From Baseline in Patients With Newly Diagnosed CML in the BOSULIF 400 mg Study Based on a Minimum of 57 Months of Follow-Up (bosutinib [all grades/grade 3/4] vs imatinib [all grades/grade 3/4]): Hematology parameters were platelet count decreased (68/14 vs 60/6); absolute neutrophil count decreased (42/9 vs 65/20); hemoglobin decreased (89/9 vs 90/7); white blood cell count decreased (50/6 vs 70/8); lymphocyte count decreased (84/12 vs 82/14). Biochemistry parameters were serum glutamic-pyruvic transaminase (SGPT)/ALT increased (68/26 vs 28/3); serum glutamic-oxaloacetic transaminase (SGOT)/AST increased (56/13 vs 29/3.4); lipase increased (53/19 vs 35/8); phosphorus decreased (54/9 vs 69/21); amylase increased (32/3.4 vs 18/2.3); alkaline phosphatase increased (41/0 vs 43/0.4); calcium decreased (55/1.5 vs 57/1.1); glucose increased (57/3 vs 65/3.4); creatine kinase increased (36/3 vs 65/5); creatinine increased (94/1.1 vs 98/0.8).

Adverse Reactions in Patients With Imatinib-Resistant or -Intolerant Ph+ CP, AP, and BP CML: The single-arm clinical trial enrolled patients with Ph+ CP, AP, or BP CML and with resistance or intolerance to prior therapy. The safety population (received at least 1 dose of BOSULIF) included 546 CML patients: 284 patients with CP CML previously treated with imatinib only who had a median duration of BOSULIF treatment of 26 months (range: 0.2 to 155 months), and a median dose intensity of 437 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 (range: 0.2 to 148 months) and a median dose intensity of 427 mg/day; and 143 patients with advanced phase (AdvP) CML, including 79 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 (range: 0.1 to 140 months) and 3 months (range: 0.03 to 71 months), respectively. The median dose intensity was 406 mg/day and 456 mg/day in the AP CML and BP CML cohorts, respectively. Serious adverse reactions occurred in 30% of patients in the safety population of the single-arm trial in patients with CML (N=546) who were resistant or intolerant to prior therapy. Serious adverse reactions reported in >2% of patients included pneumonia (7%), pleural effusion (6%), pyrexia (3.7%), coronary artery disease (3.5%), dyspnea (2.6%), rash (2.2%), thrombocytopenia (2%), abdominal pain (2%), and diarrhea (2%). Fatal adverse reactions occurred in 12 patients (2.2%) due to coronary artery disease (0.9%), pneumonia (0.4%), respiratory failure (0.4%), gastrointestinal hemorrhage (0.2%), acute kidney injury (0.2%), and acute pulmonary edema (0.2%).

Permanent discontinuation of bosutinib due to an adverse reaction occurred in 22% of patients with CML who were resistant or intolerant to prior therapy. Adverse reactions which resulted in permanent discontinuation in >2% of patients included thrombocytopenia (6%), hepatic dysfunction (3.3%), and neutropenia (2%). Dose modifications (dose interruption or reductions) of bosutinib due to an adverse reaction occurred in 66% of patients with CML who were resistant or intolerant to prior therapy. Adverse reactions which required dose interruptions or reductions in >5% of patients included thrombocytopenia (24%), diarrhea (14%), rash (13%), hepatic dysfunction (10%), neutropenia (9%), pleural effusion (8%), vomiting (7%), anemia (6%), and abdominal pain (6%). The most common adverse reactions, in ≥20% of patients in the safety population of the single-arm trial in patients with CML (N=546) who were resistant or intolerant to prior therapy were diarrhea (83%), nausea (47%), rash (46%), abdominal pain (45%), vomiting (39%), fatigue (33%), pyrexia (28%), hepatic dysfunction (27%), respiratory tract infection (24%), cough (23%), and headache (21%).

The most common laboratory abnormalities that worsened from baseline in ≥20% were creatinine increased (93%), hemoglobin decreased (91%), lymphocyte decreased (80%), platelets decreased (69%), absolute neutrophil count (54%), ALT increased (53%), calcium decreased (53%), white blood cell count decreased (52%), urate increased (48%), AST increased (47%), phosphorus decreased (39%), alkaline phosphatase increased (39%), lipase increased (28%), magnesium increased (25%), potassium decreased (24%), potassium increased (23%).

Adverse reactions (all grades [%]/Grade 3/4 [%]) with ≥10% incidence in patients with CP CML who were resistant or intolerant to prior therapy in the single-arm trial (N=403) based on long-term follow-up (based on a minimum of 105 months) were diarrhea (85/10), abdominal pain[a] (49/2), rash[b] (48/9), nausea (47/1), vomiting (38/3), fatigue (35/3), hepatic dysfunction[c] (29/11), respiratory tract infection[d] (27/<1), pyrexia (25/1), cough (24/0), headache (21/1), edema[e] (19/<1), arthralgia (19/1), constipation (15/<1), pleural effusion (14/4), back pain (14/1), decreased appetite (14/1), pruritus (12/1), dyspnea (12/2), influenza[f] (11/1), dizziness (11/0), hypertension[g] (11/3), pneumonia[h] (10/4).

Adverse reactions (all grades [%]/Grade 3/4 [%]) with ≥10% incidence in patients with AdvP CML who were resistant or intolerant to prior therapy in the single-arm trial (N=143) based on long-term follow-up were diarrhea (76/4), nausea (48/2), vomiting (43/3), rash[b] (42/5), pyrexia (37/3), abdominal pain[a] (36/7), fatigue (27/6), cough (22/0), hepatic dysfunction[c] (21/10), dyspnea (20/6), pneumonia[h] (18/12), headache (18/4), constipation (17/1), edema[e] (17/1), respiratory tract infection[d] (17/0), arthralgia (15/0), dizziness (14/1), decreased appetite (14/0), chest pain[i] (12/1).

[a]Abdominal pain includes the following preferred terms: Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness, Dyspepsia, Epigastric discomfort, Gastrointestinal pain, Hepatic pain.

[b]Rash includes the following preferred terms: Acarodermatitis, Acne, Angular cheilitis, Blister, Dermatitis, Dermatitis acneiform, Dermatitis psoriasiform, Drug eruption, Eczema, Eczema asteatotic, Erythema, Erythema annulare, Exfoliative rash, Lichenoid keratosis, Palmar erythema, Photosensitivity reaction, Pigmentation disorder, Psoriasis, Pyoderma gangrenosum, Pyogenic granuloma, Rash, Rash erythematous, Rash generalized, Rash macular, Rash maculopapular, Rash pruritic, Rash pustular, Seborrheic dermatitis, Seborrheic keratosis, Skin depigmentation, Skin discoloration, Skin disorder, Skin exfoliation, Skin hyperpigmentation, Skin hypopigmentation, Skin irritation, Skin lesion, Skin plaque, Skin toxicity, Stasis dermatitis.

[c]Hepatic dysfunction includes the following preferred terms: Alanine aminotransferase increased, Aspartate aminotransferase increased, Bilirubin conjugated increased, Blood alkaline phosphatase increased, Blood bilirubin increased, Blood bilirubin unconjugated increased, Gamma-glutamyltransferase increased, Hepatic enzyme increased, Hepatic function abnormal, Hepatic steatosis, Hepatitis toxic, Hepatomegaly, Hepatotoxicity, Hyperbilirubinemia, Liver disorder, Liver function test abnormal, Liver function test increased, Transaminases increased.

[d]Respiratory tract infection includes the following preferred terms: Nasopharyngitis, Respiratory tract congestion, Respiratory tract infection, Respiratory tract infection viral, Upper respiratory tract infection, Viral upper respiratory tract infection.

[e]Edema includes the following preferred terms: Eye edema, Eyelid edema, Face edema, Generalized edema, Localized edema, Edema, Edema peripheral, Penile edema, Periorbital edema, Periorbital swelling, Peripheral swelling, Scrotal edema, Scrotal swelling, Swelling, Swelling face, Swelling of eyelid, Testicular edema, Tongue edema.

[f]Influenza includes the following preferred terms: H1N1 influenza, Influenza.

[g]Hypertension* includes the following preferred terms: Blood pressure increased, Blood pressure systolic increased, Essential hypertension, Hypertension, Hypertensive crisis, Retinopathy hypertensive.

[h]Pneumonia includes the following preferred terms: Atypical pneumonia, Lower respiratory tract congestion, Lower respiratory tract infection, Pneumonia, Pneumonia aspiration, Pneumonia bacterial, Pneumonia fungal, Pneumonia necrotizing, Pneumonia streptococcal.

[i]Chest pain includes the following preferred terms: Chest discomfort, Chest pain.

*ADR identified postmarketing.

In the single-arm study in patients with CML who were resistant or intolerant to prior therapy, 2 patients (0.4%) experienced QTcF interval of greater than 500 msec. Patients with uncontrolled or significant cardiovascular disease, including QT interval prolongation, were excluded by protocol.

Number (%) of Patients with Clinically Relevant All Grade or Grade 3/4 Laboratory Test Abnormalities in the Safety Population of the Study of Patients With CML Who Were Resistant or Intolerant to Prior Therapy (CP [all grades/grade 3/4]; AdvP [all grades/grade 3/4]): Hematology parameters were platelet count decreased (66/26; 80/57), absolute neutrophil count decreased (50/16; 66/39), hemoglobin decreased (89/13; 97/38), lymphocyte decreased (79/14; 82/21), white blood cell count decreased (51/7; 57/27). Biochemistry parameters were SGPT/ALT increased (58/11; 39/6), SGOT/AST increased (50/5; 37/3.5), lipase increased (32/12; 19/6), phosphorus decreased (41/8; 33/7), total bilirubin increased (16/0.7; 22/2.8), creatinine increased (95/3; 87/1.4), alkaline phosphatase increased (39/0; 39/1.4), glucose increased (42/2.7; 39/6), sodium increased (23/0.5; 11/0), sodium decreased (18/2.2; 27/6), calcium decreased (55/4.7; 45/3.5), urate increased (49/6; 43/6), magnesium increased (27/7; 18/4.9), potassium decreased (22/1.7; 29/4.9), potassium increased (25/2.7; 19/2.1).

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 all 1372 patients with 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: *0.1% and less than 1%* - 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

Endocrine Disorders: *1% and less than 10%* - Hypothyroidism; *0.1% and less than 1%* - Hyperthyroidism

Gastrointestinal Disorders: *1% and less than 10%* - Gastritis, Pancreatitis (includes Edematous pancreatitis, Pancreatic enzymes increased, Pancreatitis, Pancreatitis acute, Pancreatitis chronic), Gastrointestinal hemorrhage (includes Anal hemorrhage, Gastric hemorrhage, Gastrointestinal hemorrhage, Intestinal hemorrhage, Lower gastrointestinal hemorrhage, Rectal hemorrhage, Upper gastrointestinal hemorrhage)

General Disorders and Administrative Site Conditions: *1% and less than 10%* - Pain

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%* - Bronchitis

Investigations: *1% and less than 10%* - Electrocardiogram QT prolonged (includes Electrocardiogram QT prolonged, Long QT syndrome)

Metabolism and Nutrition Disorders: *1% and less than 10%* - Dehydration

Musculoskeletal and Connective Tissue Disorders: *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 kidney injury, Renal impairment, Renal failure

Respiratory, Thoracic, and Mediastinal Disorders: *1% and less than 10%* - Pulmonary hypertension (includes Pulmonary hypertension, Pulmonary arterial hypertension, Pulmonary arterial pressure increased); *0.1% and less than 1%* - Acute pulmonary edema (includes Acute pulmonary edema, Pulmonary edema), Respiratory failure

Skin and Subcutaneous Disorders: *0.1% and less than 1%* - Erythema multiforme

Postmarketing Experience

The following additional adverse reactions have been identified during post-approval use of BOSULIF. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: Thrombotic microangiopathy

Skin and Subcutaneous Tissue Disorders: Stevens-Johnson syndrome

DRUG INTERACTIONS

Effect of Other Drugs on Bosulif

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 (PPI): 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.

USE IN SPECIFIC POPULATIONS

Pregnancy: Based on findings from animal studies and its mechanism of action, BOSULIF can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies conducted in rats and rabbits, oral administration of bosutinib during organogenesis caused adverse developmental outcomes, including structural abnormalities, embryo-fetal mortality, and alterations to growth at maternal exposures (AUC) as low as 1.2 times the human exposure at the dose of 500 mg/day. Advise pregnant women of the potential risk to a fetus. **Lactation:** No data are available regarding the presence of bosutinib or its metabolites in human milk or its effects on a breastfed child or on milk production. However, bosutinib is present in the milk of lactating rats. 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.

Females and Males of Reproductive Potential: Based on findings from animal studies, BOSULIF can cause fetal harm when administered to a pregnant woman. Females of reproductive potential should have a pregnancy test prior to starting treatment with BOSULIF. Advise females of reproductive potential to use effective contraception (methods that result in less than 1% pregnancy rates) during treatment with BOSULIF and for at least 2 weeks after the last dose. The risk of infertility in females or males of reproductive potential has not been studied in humans. Based on findings from animal studies, BOSULIF may cause reduced fertility in females and males of reproductive potential.

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

Geriatric Use: In the single-arm study in patients with CML who were resistant or intolerant to prior therapy of BOSULIF in patients with Ph+ CML, 20% were age 65 and over and 4% were 75 and over. Of the 268 patients who received bosutinib in the study for newly diagnosed CML, 20% were age 65 and over, 5% 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.

Renal Impairment: Reduce the BOSULIF starting dose in patients with moderate (creatinine clearance [CL_{cr}] 30 to 50 mL/min, estimated by Cockcroft-Gault [C-G]) and severe (CL_{cr} less than 30 mL/min, C-G) renal impairment at baseline. For patients who have declining renal function while on BOSULIF who cannot tolerate the starting dose, follow dose adjustment recommendations for toxicity. BOSULIF has not been studied in patients undergoing hemodialysis.

Hepatic Impairment: Reduce the BOSULIF dosage in patients with hepatic impairment (Child-Pugh A, B, or C).

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling. **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, break, 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. **Cardiovascular Problems:** Advise patients that cardiac failure, left ventricular dysfunction, and cardiac ischemic events have been reported. Advise patients to seek immediate medical attention if any symptoms suggestive of cardiac failure and cardiac ischemia occur, such as shortness of breath, weight gain, or fluid retention. **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. **Embryo-Fetal Toxicity:** Advise females to inform their healthcare provider if they are pregnant or become pregnant. Inform female patients of the risk to a fetus and potential loss of the pregnancy. Advise females of reproductive potential to use effective contraception during treatment and for at least 2 weeks after receiving the last dose of BOSULIF. Advise lactating women not to breastfeed during treatment with BOSULIF and for at least 2 weeks after the last dose. **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.

Rx only

This brief summary is based on BOSULIF Prescribing Information 0443-14.7, revised May 2021.

Pfizer Oncology