



# U.S. FDA Approves Pfizer's BOSULIF® (bosutinib) for the Treatment of Patients with Newly-Diagnosed Ph+ Chronic Myelogenous Leukemia (CML)

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Pfizer's Third U.S. Hematology Approval in Five Months

Pfizer Inc. (NYSE:PFE) today announced the U.S. Food and Drug Administration (FDA) approved a supplemental New Drug Application (sNDA) to expand the indication for BOSULIF® (bosutinib) to include adult patients with newly-diagnosed chronic phase Philadelphia chromosome-positive chronic myelogenous leukemia (Ph+ CML). The sNDA was reviewed and approved under the FDA's Priority Review and accelerated approval programs based on molecular and cytogenetic response rates. Continued approval for this indication may be contingent upon verification and confirmation of clinical benefit in an ongoing long-term follow up trial. BOSULIF was first approved in September 2012 in the U.S. for the treatment of adult patients with chronic, accelerated or blast phase Ph+ CML with resistance or intolerance to prior therapy.

"BOSULIF was Pfizer's first treatment for hematologic malignancies, and has since become an important treatment option for Ph+ CML patients who are resistant or intolerant to previous therapy. This expanded indication has the potential to make an even greater impact on the lives of patients with CML," said Liz Barrett, Global President, Pfizer Oncology. "Today's news marks the third FDA approval for a Pfizer hematology medicine in just five months, a significant achievement that reinforces our commitment to patients living with blood cancers."

“Among patients with CML today, with the various treatment options available, it is important to recognize the unique needs of each of my CML patients and prescribe treatments that best meet those needs,” said Jorge E. Cortes, M.D., The University of Texas MD Anderson Cancer Center. “The efficacy and distinct tolerability profile of BOSULIF make it an important and useful treatment option for newly diagnosed CML patients.”

The approval was based on results from BFORE (Bosutinib trial in First line chrOnic myelogenous leukemia tREatment), a randomized multicenter, multinational, open-label Phase 3 study which showed BOSULIF 400 mg was associated with a significantly higher rate of patients achieving major molecular response (MMR) at 12 months (47.2%; 95% CI, 40.9-53.4) compared to the rate achieved in patients treated with imatinib 400 mg (36.9%; 95% CI, 30.8-43.0), a current standard of care (two-sided P=0.0200). Complete cytogenetic response (CCyR) rate by 12 months was 77.2% (95% CI: 72.0, 82.5) for patients treated with BOSULIF compared to 66.4% (95% CI: 60.4, 72.4) for patients treated with imatinib (two-sided P=0.0075). The adverse events seen in the trial were consistent with the known safety profile for BOSULIF. The most common adverse reactions in newly diagnosed CML patients treated with BOSULIF (incidence  $\geq$ 20%) are diarrhea (70%), nausea (35%), thrombocytopenia (35%), rash (34%), increased alanine aminotransferase (ALT) (31%), abdominal pain (25%), and increased aspartate aminotransferase (AST) (23%). For more information, please see Important Safety Information for BOSULIF below.

Pfizer and Avillion entered into an exclusive collaborative development agreement in 2014 to conduct the BFORE trial. Under the terms of the agreement, Avillion provided funding and conducted the trial to generate the clinical data used to support this application and other potential regulatory filings for marketing authorization for BOSULIF as first-line treatment for patients with chronic phase Ph+ CML. With this approval, Avillion is eligible to receive milestone payments from Pfizer. Pfizer retains all rights to commercialize BOSULIF globally.

## **ABOUT CHRONIC MYELOGENOUS LEUKEMIA (CML)**

Chronic myelogenous leukemia (CML) is a rare blood cancer, which begins in the bone marrow, but often moves into the blood.<sup>1</sup> Researchers estimate that by 2020, more than 412,000 people worldwide will be diagnosed with leukemia (all types).<sup>2</sup> CML accounts for 10-15% of all incident leukemia cases.<sup>1,3</sup> In the U.S., approximately 48,000 people are living with CML.<sup>4</sup> Around 9,000 new CML cases were diagnosed in the U.S. in 2017.<sup>1</sup>

## **ABOUT BOSULIF® (bosutinib)**

BOSULIF® (bosutinib) is an oral, once-daily, tyrosine kinase inhibitor (TKI), which inhibits the Bcr-Abl kinase that promotes CML; it is also an inhibitor of Src-family kinases. In the U.S., BOSULIF (bosutinib) is now indicated for the treatment of patients with newly-diagnosed chronic phase Philadelphia chromosome-positive chronic myelogenous leukemia (Ph+ CML) and for the treatment of adult patients with chronic, accelerated or blast phase Ph+ CML with resistance or intolerance to prior therapy (first approved in September 2012). A 400 mg tablet was also recently approved by the FDA in addition to the previously approved 100 mg and 500 mg strengths. The recommended dose for newly-diagnosed patients is 400 mg orally once daily with food. For patients who are resistant or intolerant to prior tyrosine kinase inhibitor (TKI) therapy, the recommended dose is 500 mg orally once daily with food.

In Europe, BOSULIF was granted conditional marketing authorization in March 2013 for the treatment of adult patients with Ph+ CML previously treated with one or more TKIs and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options. The European Medicines Agency (EMA) has also validated for review a Type II Variation application for use of BOSULIF in the same patient population.

### **About the BFORE Study**

BFORE (Bosutinib trial in First line chrOnic myelogenous leukemia tREatment) is a randomized, multicenter, open-label Phase 3 study designed to assess the effectiveness and safety of BOSULIF® (bosutinib) as a first-line treatment for patients with chronic phase Ph+ CML. The study enrolled 536 patients at multiple sites in North America, Asia and Europe. Patients were randomized 1:1 to receive BOSULIF 400 mg or imatinib 400 mg, a standard of care, for the duration of the study. The primary outcome was to show superiority of BOSULIF over imatinib at 12 months by comparing MMR, or the proportion of patients in each arm whose levels of the Bcr-Abl1 kinase have dropped below 0.1%.

### **IMPORTANT BOSULIF® (bosutinib) SAFETY INFORMATION**

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

**Gastrointestinal Toxicity:** Diarrhea, nausea, vomiting, and abdominal pain can occur. In the randomized clinical trial of patients with newly diagnosed Ph+ CML, the median time to onset for diarrhea (all grades) among patients in the BOSULIF treatment group (n=268) was 3 days and the median duration per event was 3 days. Among 546 patients in a single-arm study of patients with CML who were resistant or intolerant to prior

therapy, median time to onset of diarrhea (all grades) was 2 days, median duration was 2 days, and the median number of episodes per patient was 3 (range 1-268). Monitor and manage patients using standards of care, including antidiarrheals, antiemetics, and/or fluid replacement. Withhold, dose reduce, or discontinue BOSULIF as necessary.

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

**Hepatic Toxicity:** Elevations in serum transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) can occur. Perform hepatic enzyme tests at least monthly for the first 3 months and as clinically indicated. In patients with transaminase elevations, monitor liver enzymes more frequently. One case consistent with drug-induced liver injury occurred without alternative causes in a trial of BOSULIF in combination with letrozole. Withhold, dose reduce, or discontinue BOSULIF as necessary. In patients with mild, moderate, or severe hepatic impairment, the recommended starting dose is 200 mg daily.

**Renal Toxicity:** An on-treatment decline in estimated glomerular filtration rate has occurred in patients treated with BOSULIF. Monitor renal function at baseline and during therapy, with particular attention to patients with preexisting renal impairment or risk factors for renal dysfunction. Consider dose adjustment in patients with baseline and treatment-emergent renal impairment.

Reduce the BOSULIF starting dose in patients with moderate (creatinine clearance [CLcr] 30 to 50 mL/min) or severe (CLcr less than 30 mL/min) 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.

**Fluid Retention:** Fluid retention can occur with BOSULIF and may cause pericardial effusion, pleural effusion, pulmonary edema, and/or peripheral edema. Among 546 patients in a single-arm study of patients with Ph+ CML who were resistant or intolerant to prior therapy, Grade 3/4 fluid retention was reported in 26 patients (5%). Monitor and manage patients using standards of care. Interrupt, dose reduce, or discontinue BOSULIF as necessary.

**Embryofetal Toxicity:** BOSULIF can cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised of the potential hazard to the fetus. Advise females of reproductive potential to use effective contraceptive measures to prevent pregnancy while being treated with BOSULIF and for at least 1 month after the

final dose.

**Adverse Reactions:** The most common adverse reactions observed in greater than or equal to 20% of patients with newly diagnosed CML were diarrhea, nausea, thrombocytopenia, rash, increased ALT, abdominal pain, and increased AST. The most common Grade 3/4 adverse reactions and laboratory abnormalities observed in greater than 10% of newly diagnosed CML patients were thrombocytopenia and increased ALT.

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

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

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

**Lactation:** Because of the potential for serious adverse reactions in a nursing child, breastfeeding is not recommended during treatment with BOSULIF and for at least 1 month after the last dose.

Please see full Prescribing Information

here. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/203341s009lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/203341s009lbl.pdf)

## **About Pfizer Oncology**

Pfizer Oncology is committed to pursuing innovative treatments that have a meaningful impact on those living with cancer. As a leader in oncology speeding cures and accessible breakthrough medicines to patients, Pfizer Oncology is helping to redefine life with cancer. Our strong pipeline of biologics, small molecules and immunotherapies, one of the most robust in the industry, is studied with precise focus on identifying and translating the best scientific breakthroughs into clinical application for patients across a wide range of cancers. By working collaboratively with academic institutions, individual researchers, cooperative research groups, governments and licensing partners, Pfizer Oncology strives to cure or control cancer with its breakthrough medicines. Because

Pfizer Oncology knows that success in oncology is not measured solely by the medicines you manufacture, but rather by the meaningful partnerships you make to have a more positive impact on people's lives.

**Pfizer Inc.: Working together for a healthier world™**

At Pfizer, we apply science and our global resources to bring therapies to people that extend and significantly improve their lives. We strive to set the standard for quality, safety and value in the discovery, development and manufacture of healthcare products. Our global portfolio includes medicines and vaccines as well as many of the world's best-known consumer healthcare products. Every day, Pfizer colleagues work across developed and emerging markets to advance wellness, prevention, treatments and cures that challenge the most feared diseases of our time. Consistent with our responsibility as one of the world's premier innovative biopharmaceutical companies, we collaborate with health care providers, governments and local communities to support and expand access to reliable, affordable health care around the world. For more than 150 years, we have worked to make a difference for all who rely on us. We routinely post information that may be important for investors to our website at [www.pfizer.com](http://www.pfizer.com). In addition, to learn more, please visit us on [www.pfizer.com](http://www.pfizer.com) and follow us on Twitter at @Pfizer and @Pfizer\_News, LinkedIn, YouTube, and like us on Facebook at [Facebook.com/Pfizer](https://www.facebook.com/Pfizer).

**DISCLOSURE NOTICE:** The information contained in this release is as of December 19, 2017. Pfizer assumes no obligation to update forward-looking statements contained in this release as the result of new information or future events or developments.

This release contains forward-looking information about BOSULIF (bosutinib), and a new indication in the U.S. for the treatment of adult patients with newly-diagnosed chronic phase Philadelphia chromosome-positive chronic myelogenous leukemia, including its potential benefits, that involves substantial risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statements. Risks and uncertainties include, among other things, the uncertainties inherent in research and development, including the ability to meet anticipated trial commencement and completion dates and regulatory submission dates, as well as the possibility of unfavorable clinical trial results, including unfavorable new clinical data and additional analyses of existing clinical data; uncertainties regarding the commercial success of BOSULIF; whether and when any applications for the new indication may be filed with regulatory authorities in any other jurisdictions; whether and when the EMA will approve the Type II Variation application for the potential new indication and whether and when regulatory authorities in any other jurisdictions may approve any such other applications

that may be pending or filed, which will depend on the assessment by such regulatory authorities of the benefit-risk profile suggested by the totality of the efficacy and safety information submitted; decisions by regulatory authorities regarding labeling and other matters that could affect the availability or commercial potential of BOSULIF, including the new indication; and competitive developments.

A further description of risks and uncertainties can be found in Pfizer's Annual Report on Form 10-K for the fiscal year ended December 31, 2016 and in its subsequent reports on Form 10-Q, including in the sections thereof captioned "Risk Factors" and "Forward-Looking Information and Factors That May Affect Future Results," as well as in its subsequent reports on Form 8-K, all of which are filed with the U.S. Securities and Exchange Commission and available at [www.sec.gov](http://www.sec.gov) and [www.pfizer.com](http://www.pfizer.com).

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1 American Cancer Society. What is Chronic Myeloid Leukemia?

<http://www.cancer.org/acs/groups/cid/documents/webcontent/003112-pdf.pdf>. Accessed August 2017.

2 GLOBOCAN Online Analysis/Prediction.

[http://globocan.iarc.fr/old/burden.asp?selection\\_pop=224900&Text-p=World&selection\\_cancer=12280&Text-c=Leukaemia&pYear=8&type=0&window=1&submit=%C2%A0Execute](http://globocan.iarc.fr/old/burden.asp?selection_pop=224900&Text-p=World&selection_cancer=12280&Text-c=Leukaemia&pYear=8&type=0&window=1&submit=%C2%A0Execute). Accessed December 2017.

3 Hochhaus, A. Educational Session: Managing Chronic Myeloid Leukemia as a Chronic Disease. American Society of Hematology. 2011; 10: 1.

4 National Cancer Institute. Surveillance Epidemiology and End Results (SEER) Cancer Stat Facts: Chronic Myeloid Leukemia (CML).

<https://seer.cancer.gov/statfacts/html/cmlyl.html>. Accessed December 2017.

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