BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

BOSULIF® (bosutinib) oral
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and/or Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**

Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Medical Necessity Requirements for BOSULIF (bosutinib)

Criteria for Initial Therapy:

Prescriber Qualifications
- Prescribed by an Oncologist or is in consultation with an Oncologist

Indication
- Accelerated phase or blast phase Philadelphia chromosome positive chronic myelogenous leukemia (Ph+ CML) resistant or intolerant to prior therapy
- Chronic phase Philadelphia chromosome positive chronic myelogenous leukemia (Ph+ CML), newly diagnosed or resistant or intolerant to prior therapy

- Other oncologic direct treatment use listed in National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A

Age Requirement
- **ONE** of the following:
  - **18 years of age or older:** Accelerated phase or blast phase Philadelphia chromosome positive chronic myelogenous leukemia
  - **1 year of age or older:** Chronic phase Philadelphia chromosome positive chronic myelogenous leukemia

Baseline Clinical Evaluation
- Confirmed diagnosis of Philadelphia chromosome positive chronic myelogenous leukemia (Ph+ CML)
- Negative pregnancy test in a woman of childbearing potential

Brand Specific Criteria
- Have failure, contraindication or intolerance with **THREE** generic equivalents (if available) for at least three months each. **Note**: Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety
- There is **NO** concurrent use with **ANY** of the following:
  - Strong or moderate cytochrome P450 3A (CYP3A) inhibitors
  - Strong CYP3A inducers
  - Proton pump inhibitors (e.g., lansoprazole, omeprazole)

Additional Requirements
- Use of Bosulif tablet with Bosulif capsule will not be approved

Documentation Requirements
- A completed request form must be submitted including:
  - Chart notes
  - Lab result
  - Supporting clinical documentation

Initial Therapy Criteria Approval Duration
- 6 months OR end of plan year

Criteria for Continuation of Therapy (renewal therapy):
Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy.

Prescriber Qualification
- Continues to be seen by an Oncologist or is in consultation with an Oncologist

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Clinical Response
- No evidence of disease progression or unacceptable toxicity

Adherence
- Adherence to the prescribed therapy regimen has been documented

Brand Specific Criteria
- Have failure, contraindication or intolerance with **THREE** generic equivalents (if available) for at least three months each. **Note**: Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety
- There is **NO** concurrent use with **ANY** of the following:
  - Strong or moderate cytochrome P450 3A (CYP3A) inhibitors
  - Strong CYP3A inducers
  - Proton pump inhibitors (e.g., lansoprazole, omeprazole)
- If clinically appropriate, withhold, reduce dose, or permanently discontinue based on severity, recurrence, persistence, or duration of the following adverse reactions:
  - Diarrhea, nausea, vomiting, abdominal pain
  - Myelosuppression (decreased absolute neutrophil count, platelets, hemoglobin)
  - Hepatotoxicity (elevated alanine aminotransferase, aspartate aminotransferase)
  - Cardiac failure, left ventricular dysfunction, cardiac ischemia
  - Fluid retention (pericardial effusion, pleural effusion, pulmonary edema, peripheral edema)
  - Renal toxicity (reduced estimated glomerular filtration rate)

Additional Requirements
- Use of Bosulif tablet with Bosulif capsule will not be approved

Documentation Requirements
- Chart notes
- Supporting clinical documentation with evidence of improvement in given indication
- Lab values that confirm safe use

Continuation Therapy Criteria Approval Duration
- 12 months OR end of plan year

Criteria for Off-Label Use Requests:

Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. Off-Label Use of Non-Cancer Medications

2. Off-Label Use of Cancer Medications

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Description:

Bosulif (bosutinib) is indicated for the treatment of adult patients with accelerated (AP) or blast phase (BP) Philadelphia chromosome-positive chronic myelogenous leukemia (Ph+ CML) resistant or intolerant to prior therapy; and for the treatment of adult and pediatric patients 1 year of age and older with chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukemia (Ph+ CML) newly diagnosed or resistant or intolerant to prior therapy.

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

Chronic myeloid leukemia (CML)

- CML is a malignant clonal disorder of hematopoietic stem cells arising from a genetic mutation that results in increased myeloid cells, and occasionally in erythroid cells, and platelets in the peripheral blood along with myeloid hyperplasia in the bone marrow

- CML is associated with the Philadelphia chromosome
  - There is a translocation between chromosomes 8 and 22 that gives rise to a *BCR-ABL1* fusion gene that produces a protein with deregulated tyrosine kinase activity

- CML occurs in three phases:
  - Chronic phase (CP-CML)
  - Accelerated phase (AP-CML)
  - Blast phase (BP-CML)

- It often presents in the chronic phase but it can progress to accelerated and ultimately to the blast phase or blast crisis
  - The prognosis for AP-CML or BP-CML is considered poor as they tend to be relatively resistant to most treatments, even after successful TKI treatment
  - Transplantation may need to be considered in such patients

- Tyrosine kinase inhibitors (TKI) are considered first-line therapy
  - Choices include imatinib, dasatinib, and nilotinib
  - Bosutinib is currently recommended for after failure of imatinib or dasatinib or nilotinib
  - TKI target the constitutively active tyrosine kinase implicated in the pathogenesis of CML
  - TKIs are the initial treatment of choice for the majority of patients with CML
  - There are no clinical trials that compare TKI to help recommend one TKI over another for individual patients

- Selection on which agent to use may be dependent on patient age and co-morbidities, risk evaluation, toxicity profile of TKI, disease phase, response to previous therapy, and Breakpoint Cluster Region Abelson Murine Leukemia (BCR-ABL) mutation profile status

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- In patients with disease progression to either AP-CML or BP-CML on prior TKI therapy, treatment with a course of an alternative TKI (one not received before) is helpful as a bridge to hematopoietic cell transplantation (HCT)

- Response during TKI therapy is the most important prognostic factor for long-term outcome in CML
  - Response is determined by
    - Measuring hematologic – normalization of peripheral blood counts
    - Cytogenetics – decrease in the number of Ph+ metaphases using bone marrow
    - Molecular responses – decrease in the amount of *BCR-ABL1* chimeric mRNA using QPCR
  - Primary resistance is when a TKI fails to achieve a desired response
  - Secondary resistance is a relapse following an initial response to a TKI

- The goal of TKI therapy is to achieve a complete cytogenetic response within 12 months of therapy and to prevent disease progression from CP-CML to accelerated or blast phase CML

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

CYP 3A4 inhibitors & inducers (not a complete listing)

Moderate inhibitors	amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit products, imatinib, and verapamil
Strong inhibitors	boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole
Moderate inducers	bosentan, efavirenz, etravirine, modafinil and nafcillin
Strong inducers	carbamazepine, phenytoin, rifampin and St. John's Wort

BCR-ABL1 (IS) Response Milestones:

BCR-ABL1 (IS)	3 months	6 months	12 months	> 12 months
> 10%	**YELLOW**	**RED**		
>1-10%	**GREEN**		**YELLOW**	**RED**
>0.1-1%	**GREEN**			**YELLOW**
≤ 0.1%	**GREEN**			

	Clinical considerations	2nd line & subsequent treatment options
Red	• Evaluate compliance & drug interactions • Mutational analysis	• Switch to alternate TKI • Evaluate for HCT
Yellow	• Evaluate compliance & drug interactions • Mutational analysis	• Switch to alternate TKI or continue same TKI or dose escalation of imatinib (to max of 800 mg) • Evaluate for HCT
Green	• Monitor response & side effects	• Continue same TKI

Accelerated Phase CML:

Modified Criteria used at MD Anderson Cancer Center (most commonly used in clinical trials)

Peripheral blood blasts ≥ 15% and < 30% Peripheral blood blasts and promyelocytes combined ≥ 30% Peripheral blood basophils ≥ 20% Platelet count ≤ 100 x 10^9/L Additional clonal cytogenetic abnormalities in Ph+ cells
Semin Hematol 1988;25:49-61 Br J Haematol 1997;99:30-35 Blood 1993;82:691-703 Blood 2002;99:1928-1937

Blast Phase CML:

World Health Organization Criteria	International Bone Marrow Transplant Registry
Blasts ≥ 20% of peripheral white blood cells or of nucleated bone marrow cells Extramedullary blast proliferation Large foci or clusters of blasts in the bone marrow biopsy	≥ 30% blasts in the blood, marrow, or both Extramedularry infiltrates or leukemic cells
NCCN Chronic myeloid leukemia. Version 1.2018, July 26, 2017	

Treatment options based on BCR-ABL1 mutation profile: (NCCN: CML, v 1.2018)

Mutation	Treatment recommendations
E255K/V, F359V/C/I or Y253H	Dasatinib
F317L/V/I/C, T315A, or V299L	Nilotinib
E255K/V, F317L/V/I/C, F359V/C/I, T315A, or Y253H	Bosutinib
T315I	Ponatinib, Omacetaxine, allogeneic HCT, or clinical trial

- Patients with disease that is resistant to primary treatment with imatinib should be treated with nilotinib, dasatinib, or bosutinib in the second-line setting.
- Patients with disease that is resistant to primary treatment with nilotinib or dasatinib could be treated with an alternative TKI (other than imatinib) in the second-line setting.
- Ponatinib is also a treatment option for patients for whom no other TKI is indicated.
- Omacetaxine is a treatment option for patients with disease that is resistant and/or intolerant to 2 or more TKIs.

Definitions for response and relapse in CML:

CHR	Complete normalization of peripheral blood counts with leukocyte count < 10 x 10^9/L Basophils < 5% Platelet count < 450 x 10^9/L No immature cells (such as myelocytes, promyelocytes, or blasts) in peripheral blood No signs & symptoms of disease, with a non-palpable spleen
CyR	Complete CyR (CCyR): no Ph+ metaphases (correlates to *BCR-ABL (IS)* 0.1-1%) Partial CyR (PCyR): 1-35% Ph+ metaphases Minor CyR: 36-65% Ph+ metaphases Minimal CyR: 66-95% Ph+ metaphases No response: > 95% Ph+ metaphases
MR	Early MR (EMR) – *BCR-ABL (IS)* ≤ 10% at 3 and 6 months Major MR (MMR) – *BCR-ABL (IS)* < 0.1% or ≥ 3 log reduction in *BCR-ABL1* mRNA from the standardized baseline, if QPCR (IS) is not available Complete MR (CMR) – is variably described, and is best defined by the assay's level of sensitivity (such as MR 4.5)
Relapse	Any sign of loss of response defined as hematologic or cytogenetic 1 log increase in *BCR-ABL1* transcript levels with loss of MMR should prompt bone marrow evaluation for loss of CCyR but is not itself defined as relapse (hematologic or cytogenetic relapse)

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CHR: complete hematologic response CyR: cytogenetic response MR: molecular response IS: International scale – the ratio of the BCR-ABL1 transcriptions to ABL1 transcripts

Molecular response International Scale:

	International Scale (IS)
MR 2	Detectable disease at a level of ≤1 percent on the IS (≥2 log reduction from the standardized baseline). This level of response roughly corresponds to a "complete cytogenetic response"
MR 3	Detectable disease at a level of ≤0.1 percent on the IS (≥3 log reduction from the standardized baseline). This level of response has been termed a "major molecular response"
MR 4	Either detectable disease at a level of ≤0.01 percent on the IS (≥4 log reduction) **or** undetectable disease in cDNA with ≥10,000 ABL1 transcripts. This level of response requires that the assay being used is sensitive enough to detect a single abnormal transcript amongst 10,000 normal ABL1 transcripts
MR 4.5	Either detectable disease at a level of ≤0.0032 percent on the IS (≥4.4 log reduction) **or** undetectable disease in cDNA with ≥32,000 ABL1 transcripts. This level of response requires that the assay being used is sensitive enough to detect a single abnormal transcript amongst 32,000 normal ABL1 transcripts

Monitoring Response to TKI Therapy and Mutational Analysis:

Test	Recommendation
Bone marrow cytogenetic	• At diagnosis • Failure to reach response milestone • Any signs of loss of response (defined as hematologic or cytogenetic relapse
Quantitative RT-PCT (qPCR) using IS	• At diagnosis • Every 3 months after initiating treatment. After *BCR-ABL1* (IS) ≤ 1 % (> 0.1-1%) has been achieved, every 3-months x 2 y and every 3-6 months thereafter • If there is a 1-log increase in *BCR-ABL1* transcript levels with MMR, qPCR should be repeated in 1-3 months
BCR-ABL1 kinase domain mutation analysis	• Chronic phase ➢ Failure to reach response milestone ➢ Any signs of loss of response (defined as hematologic or cytogenetic relapse ➢ 1-log increase in *BCR-ABL1* transcript levels and loss of MMR • Disease progression to accelerated or blast phase

NCCN recommendation definitions:

Category 1:
Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A:
Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B:
Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3:
Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

Resources:

Bosulif (bosutinib) product information, revised by Pfizer Laboratories Div Pfizer, Inc. 12-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 10, 2025.

ORIGINAL EFFECTIVE DATE: 01/01/2016 | ARCHIVE DATE: | LAST REVIEW DATE: 02/19/2026 | LAST CRITERIA REVISION DATE: 02/19/2026

Van Etten RA, Atallah E. Chronic myeloid leukemia: Pathogenesis, clinical manifestations, and diagnosis. In: UpToDate, Larson RA, Rosmarin AG (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through December 2025. Topic last updated April 23, 2025. Accessed January 02, 2026.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Chronic Myeloid Leukemia Version 1.2026 – Updated July 16, 2025. Available at https://www.nccn.org. Accessed January 02, 2026.

Off Label Use of Cancer Medications: A.R.S. §§ 20-826(R) & (S). Subscription contracts; definitions.

Off Label Use of Cancer Medications: A.R.S. §§ 20-1057(V) & (W). Evidence of coverage by health care service organizations; renewability; definitions.