PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

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Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

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Criteria:

- **Criteria for initial therapy:** Bosulif (bosutinib) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Oncologist

  2. Individual is 18 years of age or older

  3. A confirmed diagnosis of **ONE** of the following:
     a. Newly-diagnosed chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukemia (Ph+ CML).

     b. Chronic phase (CP), accelerated phase (AP), or blast phase (BP) Ph+ CML with resistance or intolerance to prior therapy

     c. Other request for a specific oncologic direct treatment use that is found and listed in the National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A

  4. There are no significant interacting drugs

  Initial approval duration: 6 months

Criteria for continuation of coverage (renewal request): Bosulif (bosutinib) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Oncologist

2. The condition has not worsened while on therapy
   a. Worsening is seen as:
      i. Failed to achieve or maintain a complete hematologic response (peripheral blood counts have not normalized)
      ii. Failure to achieve a complete cytogenetic response (there are > 1% Ph+ metaphases in the bone marrow) at 12 months
      iii. Failure to achieve an early molecular response (*BCR-ABL (IS)* $\geq$ 10% at 6 months)
      iv. Loss of response after a previous cytogenetic or hematologic response
      v. Presence of a genetic mutation in the BCR-ABL gene associated with TKI resistance

3. Individual has been adherent with the medication

4. Individual has not developed any significant adverse drug effects that may exclude continued use, such as:
   a. Myelosuppression (decreased ANC, platelets)

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b. Diarrhea
c. Hepatotoxicity (liver test abnormalities)
d. Cardiac failure and cardiac ischemia
e. Fluid retention (pericardial effusion, pleural effusion, pulmonary edema, peripheral edema)
f. Renal toxicity (reduced eGFR)

5. There are no significant interacting drugs

Renewal duration: 12 months

- 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**

Description:

Bosulif (bosutinib) is indicated for the treatment of adult patients with chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML) with resistance or intolerance to prior therapy; and for the treatment of adult patients with newly-diagnosed chronic phase Ph+ chronic myelogenous leukemia (CML).

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)

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- 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

- 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:

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

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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.

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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 define 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)
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

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	➢ 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

Resources:

Bosulif (bosutinib) product information, revised by Pfizer Laboratories Div Pfizer, Inc. 10-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 29, 2021.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Chronic Myeloid Leukemia Version 2.2022 – Updated November 15, 2021. Available at https://www.nccn.org. Accessed November 29, 2021.

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.