BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 1/01/16**
SECTION: DRUGS	**LAST REVIEW DATE: 3/15/18**
	LAST CRITERIA REVISION DATE: 3/15/18
	ARCHIVE DATE:

BOSULIF® (bosutinib) oral tablet

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.**

BOSULIF® (bosutinib) oral tablet (cont.)

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)

- 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

BOSULIF® (bosutinib) oral tablet (cont.)

- 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

***Accelerated Phase CML*:**

Modified Criteria used at MD Anderson Cancer Center (most commonly used in clinical trials)
Peripheral blood blasts $\geq$ 15% and < 30% Peripheral blood blasts and promyelocytes combined $\geq$ 30% Peripheral blood basophils $\geq$ 20% Platelet count $\leq$ 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

BOSULIF® (bosutinib) oral tablet (cont.)

***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 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	

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

Bosulif (bosutinib)

Medication class:
Antineoplastic agent, BRC-ABL tyrosine kinase inhibitor

FDA-approved indication(s):
- Treatment of adult patients with newly-diagnosed chronic phase Ph+ chronic myelogenous leukemia (CML). This indication is approved under accelerated approval 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.
- 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

Recommended Dose:
- Newly-diagnosed chronic phase Ph+ CML: 400 mg orally once daily with food.
- Chronic, accelerated, or blast phase Ph+ CML with resistance or intolerance to prior therapy: 500 mg once daily, consider 600 mg once daily in patients who do not reach complete hematologic response by week 8 or complete cytogenetic response by week 12 and do not have Grade 3 or greater adverse reactions and who are currently taking 500 mg once daily.

Maximum dosage
- 600 mg once daily

Available Dosage Forms:
- 100 mg, 400 mg, and 500 mg tablets

BOSULIF® (bosutinib) oral tablet (cont.)

Warnings and Precautions:

- Starting dose is 200 mg in a patient with any baseline hepatic impairment, but there is no clinical data for efficacy at a dose of 200 mg once daily in patients with hepatic impairment
- With liver transaminases > 5x institutional ULN, hold until recovery to ≤ 2.5x IULN & resume at lower dose of 400 mg once daily, if recovery takes longer than 4 weeks stop Bosulif
- With transaminases ≥ 3x IULN with bilirubin > 2x IULN and ALP < 2x IULN (Hy's law case definition), stop Bosulif
- Individuals who have ≥ 7 stools/day, hold until resolves to Grade ≤ 1, resume a reduced Bosulif dose, or discontinue
- Discontinuation must be done by a professional knowledgeable on TKI discontinuation as some patients experience significant adverse effects believed to be due to TKI discontinuation
- Reduce starting dose in moderate (CrCl 30-50 mL/min) or severe (CrCle < 30 mL/min) renal impairment
- It has not been studied in individual undergoing hemodialysis
- Avoid moderate or strong CYP3A4 inducers
- Avoid moderate or strong CYP3A4 inhibitors
- Avoid proton pump inhibitors, consider short-acting antacids or H2 receptor antagonists
- Woman of child bearing potential should use effective contraception
- Woman who is breast feeding an infant or child should stop breast feeding

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 an Oncologist

2. Individual is 18 years of age or older

3. A confirmed diagnosis of **ONE** of the following:
   - Newly-diagnosed chronic phase Ph+ chronic myelogenous leukemia (CML)
   - Chronic phase, accelerated phase, or blast phase Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia (CML)

4. Philadelphia chromosome testing is positive for the Breakpoint Cluster Region Abelson Murine Leukemia (BCR-ABL) 1 fusion gene

5. BCR-ABL1 mutation profile shows individual does not have the T3151 or V299L mutation

6. Individual has failure, contraindication or intolerance to **ONE** prior tyrosine kinase therapy
   - Prior tyrosine kinase therapy includes:
     - Gleevec (imatinib)
     - Sprycel (dasatinib)
     - Tasigna (nilotinib)

BOSULIF® (bosutinib) oral tablet (cont.)

7. There are **NO** contraindications.
    - Contraindications include:
        - Hypersensitivity to Bosulif (bosutinib)

Initial approval duration:
- Newly-diagnosed chronic phase Ph+ CML: 400 mg/day x 6 months
- Chronic, accelerated, or blast phase Ph+ CML with resistance or intolerance to prior therapy: Up to 600 mg/day x 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. Continues to be seen by an Oncologist

2. The condition has not worsened while on therapy
    - Worsening is seen as:
        - Failed to achieve or maintain a complete hematologic response (peripheral blood counts have not normalized)
        - Failure to achieve a complete cytogenetic response (there are > 1% Ph+ metaphases in the bone marrow) at 12 months
        - Failure to achieve an early molecular response (*BCR-ABL (IS)* ≥ 10% at 6 months)
        - Loss of response after a previous cytogenetic or hematologic response
        - 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 contraindications or other significant level 4 adverse drug effects that may exclude continued use, such as:
    - Myelosuppression (decreased ANC, platelets)
        - Signs & symptoms may include: fever, chills, infection, unexplained easy bruising, unexplained bleeding, unexplained weakness or shortness of breath
    - Diarrhea
        - Signs & symptoms may include: diarrhea > 7 loose stools per day, nausea, vomiting, abdominal pain, blood in stools
    - Hepatotoxicity (liver test abnormalities)
        - Signs & symptoms may include: abdominal pain, bruising, yellow skin or eyes, dark brown urine, severe nausea or vomiting, fatigue, light colored stools
    - Fluid retention (pericardial effusion, pleural effusion, pulmonary edema, peripheral edema)
        - Signs & symptoms may include: swelling weight gain, shortness of breath
    - Renal toxicity (reduced eGFR)
        - Signs & symptoms may include: frequent urination, less frequent urination, abnormal small volume urination, abnormal large volume of urination

5. There are no significant interacting drugs

BOSULIF® (bosutinib) oral tablet (cont.)

Renewal duration:
- Newly-diagnosed chronic phase Ph+ CML: 400 mg/day x 6 months
- Chronic, accelerated, or blast phase Ph+ CML with resistance or intolerance to prior therapy: Up to 600 mg/day x 6 months

Resources:

Bosulif. Package Insert. Revised by manufacturer 11/2014. Accessed 09-04-2015.

Bosulif. Package Insert. Revised by manufacturer 04/2016. Accessed 10-19-2016.

Bosulif. Package Insert. Revised by manufacturer 12/2017. Accessed 02-23-2018.

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.

NCCN Clinical Practice Guidelines in Oncology: Chronic myeloid leukemia. Version 02.2018, Oct 19, 2017. https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf

UpToDate: Overview of the treatment of chronic myeloid leukemia. Current through Aug 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/overview-of-the-treatment-of-chronic-myeloid-leukemia?source=search_result&search=chronic%20myeloid%20leukemia&selectedTitle=2~150

UpToDate: Initial treatment of chronic myeloid leukemia in chronic phase. Current through Aug 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/initial-treatment-of-chronic-myeloid-leukemia-in-chronic-phase?source=see_link#H15

UpToDate: Treatment of chronic myeloid leukemia in chronic phase after failure of initial therapy. Current through Aug 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/treatment-of-chronic-myeloid-leukemia-in-chronic-phase-after-failure-of-initial-therapy?source=search_result&search=chronic%20myeloid%20leukemia&selectedTitle=4~150

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Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.
REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information

Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:

Prescribing Provider Information

Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	

Dispensing Pharmacy Information

Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:

Requested Medication Information

Medication Name:	Strength:	Dosage Form:
Directions for Use:	Quantity: / Refills:	Duration of Therapy/Use:

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

Clinical Information

1. **What is the diagnosis? Please specify below.**

   ICD-10 Code: _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy

5. **Are there any supporting labs or test results? Please specify below.**

Date	Test	Value

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Pharmacy Prior Authorization Request Form

6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: Date:

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.