09-J1000-84

Original Effective Date: 02/15/13

Reviewed: 01/09/19

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Subject: Bosutinib (Bosulif®) Tablets

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Bosutinib (Bosulif) is a second-generation dual tyrosine kinase inhibitor (TKI), and exerts is therapeutic effects by inhibiting the BCR-ABL kinase that promotes chronic myelogenous leukemia (CML) and Src-family kinases. Bosutinib has demonstrated activity against many of the BCR-ABL kinase domain mutations resistant to imatinib (Gleevec), dasatinib (Sprycel), and nilotinib (Tasigna), except V299L and T315I. Bosutinib was given orphan designation status in 2009 for the treatment of CML and was approved by the US Food and Drug Administration (FDA) in September 2012 for the treatment of adults with chronic phase, accelerated phase, or blast phase Philadelphia (Ph) chromosome-positive CML (CP-CML, AP-CML, and BP-CML, respectively) demonstrating resistance or intolerance to prior therapy. In December 2017, the indication was expanded to include the treatment of adult patients with newly-diagnosed, Ph-positive CP-CML. The newer indication was approved under accelerated approval based on molecular and cytogenetic response rates, and continued approval for this indication may be contingent upon verification and confirmation of clinical benefit in an ongoing long-term, follow-up trial.

The initial FDA-approval for previously treated patients was based principally on a single-arm, open-label, multicenter study that enrolled a total of 546 adult subjects diagnosed with CP-CML, AP-CML, or BP-CML. All subjects were previously treated with one prior TKI (imatinib) or more than one TKI (imatinib followed by dasatinib and/or nilotinib) and were imatinib resistant or intolerant. The primary endpoint was major cytogenetic response (MCyR) at 24 weeks for subjects with CP-CML and complete hematologic response (CHR) at 48 weeks for subjects with AP-CML and BP-CML. A total of 506 patients were considered evaluable for cytogenetic or hematologic efficacy assessment. In the cohort of CP-CML subjects previously treated with imatinib alone (n=262), 40.1% achieved MCyR at 24 weeks. In the cohort of CP-CML subjects who were pretreated with more than one TKI (n=112), 25.9% achieved MCyR at 24

weeks. In patients with AP-CML (n=72), 30.6% achieved CHR at week 48, and in patients with BP-CML (n=60), 16.7% achieved CHR at week 48.

The safety and efficacy of Bosulif in patients with newly-diagnosed chronic phase Ph+ CML was evaluated in the **B**osutinib trial in **F**irst-line chr**O**nic myelogenous leukemia t**RE**atment (BFORE) trial. The BFORE Trial is a 2-arm, open-label, randomized, multicenter trial comparing bosutinib 400 mg once daily alone (n=268) compared with imatinib 400 mg once daily alone (n=268) in adult patients with newly-diagnosed CP Ph+ CML. All patients are being treated and/or followed for up to 5 years. Efficacy was evaluated in the modified intent-to-treat (mITT) population. The major efficacy outcome measure was Major Molecular Response (MMR) at 12 months defined as ≤0.1% BCR-ABL ratio. Additional efficacy outcomes included CCyR by 12 months. After a minimum of 12 months of follow-up, 77.6% of the 246 bosutinib-treated patients and 72.4% of the 239 imatinib-treated patients were still receiving treatment. The median treatment duration was 14.3 months for bosutinib and 13.8 months for imatinib. The MMR at month 12 was 47.2% for bosutinib versus 36.9% for imatinib (p=.02). The CCyR at month 12 was 77.2% for bosutinib versus 66.4% for imatinib (p=.0075). The adverse effects of diarrhea, abdominal pain, thrombocytopenia, rash, and elevated liver transaminases occurred more frequent in bosutinib-treated patients, while neutropenia occurred more often in imatinib-treated patients.

Chronic myelogenous leukemia is a hematopoietic stem cell disease characterized by a reciprocal translocation between chromosomes 9 and 22, resulting in the formation of the Philadelphia chromosome. CML occurs in three different phases (i.e., chronic, accelerated, and blast phase) and is usually diagnosed in the chronic phase. Untreated chronic phase CML will eventually progress to advanced phase disease in 3 to 5 years. The National Comprehensive Cancer Network (NCCN) guidelines provide treatment recommendations for all three phases. The NCCN guidelines for CML (Version 1.2019) list imatinib, bosutinib, nilotinib, and dasatinib as category 1 options for the initial first-line treatment of chronic-phase CML in patients with a low-risk Sokal or Hasford score. For CP-CML patients with an intermediate- or high-risk score, imatinib is listed as category 2A option, while bosutinib, nilotinib, and dasatinib (second-generation TKIs) are listed as category 1 options. In addition, bosutinib, dasatinib and nilotinib have a footnote stating “Based on long-term follow-up data from the DASISION and ENESTnd trials and preliminary data from the BFORE trial, second generation TKIs (dasatinib, nilotinib, or bosutinib) are preferred for patients with an intermediate- or high-risk Sokal or Hasford score, especially for young women whose goal is to achieve a deep and rapid molecular response and eventual drug discontinuation of TKI therapy for fertility purposes.” The imatinib listing for intermediate- or high-risk scores includes a footnote stating, “Imatinib may be preferred for older patients with comorbidities such as cardiovascular disease.” Age, toxicity profile of the TKI, tolerance of adverse effects, and comorbid conditions also may affect initial choice of treatment. Allogenic hematopoietic cell transplantation (HCT) is no longer recommended as first-line treatment option for patient with CP-CML. If the 3-month response milestone (i.e., early molecular response) is not achieved after first-line TKI therapy, patients are considered to be a high risk for disease progression and alternative treatment options should be considered. Evaluation for allogenic HCT is recommended if the response milestones are not achieved at 3, 6, and 12 months. For patients who do not achieve response milestone or those with a loss of response, BCR-ABL1 mutational analysis is recommended, as it is helpful in the selection of subsequent TKI therapy.

Acute lymphoblastic leukemia (ALL) is a heterogeneous hematologic disease characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood and other organs. The long-term prognosis for adults with ALL remains poor, with cure rates of only 30% to 40%. The treatment approach to ALL represents one of the most complex and intensive programs in cancer therapy. In general, treatment phases can be largely grouped into induction, consolidation, and maintenance. During

the past decade, the advent of novel agents targeted to specific genetic abnormalities, such as those associated with Ph+ ALL, or to specific cell antigens, has contributed to improvements in outcomes in some subtypes of ALL. These agents include BCR-ABL selective TKIs for Ph+ ALL (e.g., imatinib, dasatinib, and nilotinib). Although TKIs have improved the prognosis for adults with ALL, resistance has been observed and is attributed, at least partly, to the presence of point mutations (e.g., T315I, V299L, and F317L mutations) with the ABL kinase domain. Second generation TKIs, specifically, dasatinib and nilotinib, have shown greater potency in inhibiting BCR-ABL compared with imatinib and retention of anti-leukemic activity in cells with certain imatinib-resistant ABL mutations. However, both agents are rendered inactive in persons with a T315I mutation. The NCCN guidelines for ALL (Version 1.2018) list bosutinib as a category 2A treatment option for relapsed or refractory Ph+ ALL in patients with E255K/V, F317L/V/I/C, F359V/C/I, T315A, or Y253H BCR-ABL1 mutations.

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of bosutinib (Bosulif) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1", "2", "3", and "4"):

1. Member is **NOT** taking another tyrosine kinase inhibitor (TKI) (i.e., imatinib, dasatinib, nilotinib, or ponatinib) or omacetaxine mepesuccinate (Synribo) concurrently with bosutinib.
2. Dosage of bosutinib does not exceed 600 mg daily, and will be achieved using the fewest number of tablets per day.
3. Member does **NOT** have a T315I or V299L mutation (only applicable if a BCR-ABL kinase domain mutation analysis has been performed).
4. The member is receiving treatment for **ANY** of the following conditions ("a", "b", or "c"), and **ALL** conditions-specific criteria are met:
    a. Chronic-, accelerated- or blast-phase Philadelphia (Ph) chromosome-positive or BCR-ABL1-positive chronic myeloid leukemia (CML) (including post-transplant relapse), and **EITHER** of the following ("i" or "ii"):
        i. Member has an intermediate- or high-risk Sokal or Hasford score as determined prior to treatment initiation (at least one calculated score must be provided)
        ii. Member has previously tried imatinib, dasatinib, or nilotinib, and **EITHER** had an inadequate initial treatment response or relapse during treatment, **OR** had persistent intolerable adverse effects despite appropriate dose modification (the specific adverse effect must be provided), **UNLESS** either of the following apply:
            - Member has an E255K/V, F317L/V/I/C, F359V/C/I, T315A, or Y253H BCR-ABL1 mutation (confirmatory laboratory documentation of the mutation must be submitted).
            - Member has FDA-labeled contraindications to imatinib, dasatinib, and nilotinib (the specific contraindication must be provided)

b. Relapsed or refractory Ph-positive or BCR-ABL1-positive acute lymphoblastic leukemia (ALL), **AND** the member has an E255K/V, F317L/V/I/C, F359V/C/I, T315A, or Y253H BCR-ABL1 mutation (confirmatory laboratory documentation of the mutation must be submitted).

c. An FDA-approved or NCCN-supported diagnosis (not previously listed above), and **EITHER** of the following is met ("i" or "ii"):

   i. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) **AND** member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert)

   ii. Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation

Approval duration: 6 months

Continuation of bosutinib (Bosulif) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "5"):

1. The member has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of CML, ALL, or other FDA-approved or NCCN-supported diagnosis, **OR** the member has previously met all indication-specific criteria.
2. Member does **NOT** have a T315I or V299L mutation (only applicable if a BCR-ABL kinase domain mutation analysis has been performed).
3. Member's disease has not progressed during treatment with bosutinib.
4. Member is **NOT** taking another TKI (i.e., imatinib, dasatinib, nilotinib, or ponatinib) or omacetaxine concurrently.
5. Dosage of bosutinib does not exceed 600 mg daily and will be achieved using the fewest number of tablets per day.

Approval duration: 1 year

NOTE: Quest Diagnostics® can perform the BCR-ABL kinase domain mutation analysis. Current NCCN guidelines recommend checking mutational analysis in the following situations: if there is inadequate initial response, any sign of loss of response, and in disease progression to accelerate-phase or blast-phase CML (CML-AP and CML-BP, respectively).

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved: bosutinib is indicated for: (1) the treatment of adult patients with chronic-phase, accelerated-phase, or blast-phase Ph+ CML with resistance or intolerance to prior therapy, and (2) the treatment of adult patients with newly-diagnosed, chronic-phase Ph+ CML. The second indication was approved under accelerated approval based on molecular and cytogenetic response rates, and continued approval for this indication may be contingent upon verification and confirmation of clinical benefit in an ongoing long-term, follow-up trial. The recommended dose and schedule of bosutinib is 400 mg orally

once daily with food for newly-diagnosed CML, and 500 mg orally once daily with food for CML with resistance or intolerance to prior therapy. Continue treatment with bosutinib until disease progression or member intolerance. In clinical studies of adult Ph+ CML patients, dose escalation by increments of 100 mg once daily to a maximum of 600 mg once daily was allowed in patients who did not achieve or maintain a hematologic, cytogenetic, or molecular response and who did not have Grade 3 or higher adverse reactions at the recommended starting dosage.

Dose Modifications

- **Hepatic Impairment:** In patients with pre-existing mild, moderate, and severe hepatic impairment, the recommended dose of bosutinib is 200 mg daily.
- **Renal Impairment:** In patients with pre-existing moderate renal impairment (CrCl 30 to 50 mL/min), the recommended dose of bosutinib is 300 mg daily for new-diagnosed CML and 400 mg daily for previously-treated CML. In patients with pre-existing severe renal impairment (CrCl less than 30 mL/min), the recommended dose of bosutinib is 200 mg daily for new-diagnosed CML and 300 mg daily for previously-treated CML.
- **Toxicity:**
    - Elevated liver transaminases: If elevations in liver transaminases greater than 5×institutional upper limit of normal (ULN) occur, withhold bosutinib until recovery to less than or equal to 2.5×ULN and resume at 400 mg once daily thereafter. If recovery takes longer than 4 weeks, discontinue treatment. If transaminase elevations greater than or equal to 3×ULN occur concurrently with bilirubin elevations greater than 2×ULN and alkaline phosphatase less than 2×ULN (Hy's law case definition), discontinue treatment.
    - Diarrhea: For NCI CTCAE Grade 3-4 diarrhea (increase of greater than or equal to 7 stools/day over baseline/pretreatment), withhold bosutinib until recovery to Grade less than or equal to 1. Treatment may be resumed at 400 mg once daily.
    - For other clinically significant, moderate or severe non-hematological toxicity, withhold bosutinib until the toxicity has resolved, then consider resuming at a dose reduced by 100 mg taken once daily. If clinically appropriate, consider re-escalating the dose to the starting dose taken once daily. Doses less than 300 mg/day have been used in patients; however, efficacy has not been established.
    - Neutropenia and thrombocytopenia: ANC less than $1,000\times10^6$/L or platelets less than $50,000\times10^6$/L: Withhold bosutinib until ANC greater than or equal to$1,000\times10^6$/L and platelets greater than or equal to $50,000\times10^6$/L. Resume treatment at the same dose if recovery occurs within 2 weeks. If blood counts remain low for greater than 2 weeks, upon recovery, reduce dose by 100 mg and resume treatment. If cytopenia recurs, reduce dose by an additional 100 mg upon recovery and resume treatment. Doses less than 300 mg/day have been used in patients; however, efficacy has not been established.

Drug Availability: bosutinib is supplied as 100 mg, 400 mg, and 500 mg tablets.

PRECAUTIONS:

CONTRAINDICATIONS

- Hypersensitivity to bosutinib.

WARNINGS

- **Concomitant Use With CYP3A Inhibitors and Inducers:** Avoid the concomitant use of bosutinib with strong or moderate CYP3A inhibitors **OR** strong CYP3A inducers

- Strong CYP3A inhibitors - ritonavir, indinavir, nelfinavir, saquinavir, ketoconazole, boceprevir, telaprevir, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, nefazodone and conivaptan
- Moderate CYP3A inhibitors - fluconazole, darunavir, erythromycin, diltiazem, atazanavir, aprepitant, amprenavir, fosamprevir, crizotinib, imatinib, verapamil, grapefruit products and ciprofloxacin
- Strong CYP3A inducers - rifampin, phenytoin, carbamazepine, St. John's Wort, rifabutin and phenobarbital

- **Gastrointestinal Toxicity:** Diarrhea, nausea, vomiting, and abdominal pain occur with bosutinib treatment. Monitor and manage members using standards of care, including antidiarrheals, antiemetics, and/or fluid replacement. Withhold dose, dose reduce or discontinue bosutinib as necessary.
- **Myelosuppression:** Thrombocytopenia, anemia and neutropenia occur with bosutinib treatment. Members with CML who are receiving bosutinib should have a complete blood count performed weekly for the first month and then monthly thereafter, or as clinically indicated. To manage myelosuppression, withhold, dose reduce, or discontinue bosutinib as necessary.
- **Hepatic Toxicity:** Bosutinib may cause elevations in serum transaminases (alanine aminotransferase [ALT], aspartate aminotransferase [AST]). Perform at least monthly hepatic enzyme tests for the first three months of treatment with bosutinib and as clinically indicated thereafter. In members with transaminase elevations, monitor liver enzymes more frequently. Withhold, dose reduce, or discontinue bosutinib as necessary.
- **Renal Toxicity**: An on-treatment decline in estimated glomerular filtration rate (eGFR) has occurred in patients treated with bosutinib. Monitor patients for renal function at baseline and during therapy.
- **Fluid Retention:** Fluid retention occurs with bosutinib and may manifest as pericardial effusion, pleural effusion, pulmonary edema, and/or peripheral edema. Monitor and manage members using standards of care. Interrupt, dose reduce or discontinue bosutinib as necessary.
- **Embryofetal toxicity:** May cause fetal harm. Females of reproductive potential should avoid becoming pregnant while being treated.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J8999	Prescription drug, oral, chemotherapeutic, nos

ICD-10 Diagnosis Codes That Support Medical Necessity

C92.10	Chronic myeloid leukemia, bcr/abl-positive, not having achieved remission
C92.11	Chronic myeloid leukemia, bcr/abl-positive, in remission
C92.12	Chronic myeloid leukemia, bcr/abl-positive, in relapse
C91.00	Acute lymphoblastic leukemia not having achieved remission
C91.01	Acute lymphoblastic leukemia, in remission
C91.02	Acute lymphoblastic leukemia, in relapse

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

DEFINITIONS:

Accelerated Phase CML: is a phase of chronic myelogenous leukemia in which the disease is progressing.

Acute lymphoblastic leukemia: an aggressive (fast-growing) type of leukemia (blood cancer) in which too many immature white blood cells are found in the blood and bone marrow. Also called acute lymphocytic leukemia and ALL.

Blast Phase CML: is the final phase in the evolution of CML, and behaves like an acute leukemia, with rapid progression and short survival.

Chronic Phase CML: approximately 85% of members with CML are in the chronic phase at the time of diagnosis. During this phase, members are usually asymptomatic or have only mild symptoms of fatigue, left side pain, joint and/or hip pain, or abdominal fullness.

Chronic Myelogenous Leukemia (CML): also known as chronic granulocytic leukemia (CGL), is a cancer of the white blood cells. It is a form of leukemia characterized by the increased and unregulated growth of predominantly myeloid cells in the bone marrow and the accumulation of these cells in the blood.

Cytogenetic: is a branch of genetics that is concerned with the study of the structure and function of the cell, especially the chromosomes. It includes routine analysis of G-banded chromosomes, other cytogenetic banding techniques, as well as molecular cytogenetics such as fluorescent in situ hybridization (FISH) and comparative genomic hybridization (CGH).

Induction Chemotherapy: the use of drug therapy as the initial treatment for patients presenting with advanced cancer that cannot be treated by other means.

Philadelphia chromosome or Philadelphia translocation: is a specific chromosomal abnormality that is associated with chronic myelogenous leukemia (CML).

RELATED GUIDELINES:

Allogeneic Bone Marrow and Stem Cell Transplantation, 02-38240-01

Cytogenetic Studies (Chromosomal Studies), 05-82000-18

Dasatinib (Sprycel) Tablets, 09-J1000-43

Imatinib Mesylate (Gleevec) Tablets, 09-J1000-46

Immune Globulin Therapy, 09-J0000-06

Nilotinib (Tasigna) Capsules, 09-J1000-48

Omacetaxine (Synribo) Injection, 09-J1000-87

Ponatinib (Iclusig) Tablet, 09-J1000-89

OTHER:

CML Risk Scores

Study	Calculation	Risk Definition by Calculation
Sokal et al, 1984	Exp 0.0116 x (age in years – 43.4) + (spleen – 7.51) + 0.188 x [(platelet count/700)^2 – 0.562] + 0.0887 x (blast cell -2.10)	• Low: <0.8 • Intermediate: 0.8 to 1.2 • High: >1.2
Hasford et al, 1998	0.666 when age ≥50 years + (0.042 x spleen) + 1.0956 when platelet count >1,500 x 10^3/L + (0.0584 x blast cells) + 0.20399 when basophils >3% + (0.0413 X eosinophils) x 100	• Low: ≤780 • Intermediate: 781 to 1,480 • High: >1,480

Age is in years. Spleen is in centimeters below the costal margin (maximum distance). Blast cells, eosinophils, and basophils are in percents of peripheral blood differential. All factors must be collected prior to any treatment.

Online risk calculator can be found at: http://www.icsg.unibo.it/rrcalc.asp

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 01/09/19.

GUIDELINE UPDATE INFORMATION:

02/15/13	New Medical Coverage Guideline.
03/15/14	Review and revision to guideline; consisting of reformatting position statement, updating dosage/administration, references, program exceptions, and related guidelines.
03/15/15	Review and revision to guideline; consisting of revising position statement, and updating the description, dosage/administration, and references.
11/01/15	Revision: ICD-9 Codes deleted.
03/15/16	Review and revision to guideline consisting of description, position statement, definitions, and references.
03/15/17	Review and revision to guideline consisting of removal of the age requirement and acute lymphoblastic leukemia (ALL) indication in the position statement, and updates to description section, dosage/administration section, precautions section, billing/coding section, definitions, and references.
02/15/18	Review and revision to guideline consisting of updates to description, dosage/administration, position statement, billing/coding, other, and references sections.
02/15/19	Review and revision to guideline consisting of updates to description, position statement, definitions, and references sections.