POLICY NUMBER UM ONC_1221	SUBJECT Bosulif™ (bosutinib)		DEPT/PROGRAM UM Department	PAGE 1 OF 4
DATES COMMITTEE REVIEWED 10/03/12, 02/12/14, 01/13/16, 12/30/16, 12/13/17, 11/14/18, 11/13/19, 12/11/19	APPROVAL DATE December 11, 2019	EFFECTIVE DATE December 11, 2019	COMMITTEE APPROVAL DATES (latest version listed last) 10/03/12, 02/12/14, 01/13/16, 12/30/16, 12/13/17, 11/14/18, 11/13/19, 12/11/19	
PRIMARY BUSINESS OWNER: UM APPROVED BY: Dr. Andrew Hertler		COMMITTEE/BOARD APPROVAL Utilization Management Committee		
URAC STANDARDS HUM 1		NCQA STANDARDS UM 2	ADDITIONAL AREAS OF IMPACT	
CMS REQUIREMENTS	STATE/FEDERAL REQUIREMENTS		APPLICABLE LINES OF BUSINESS All	

I. PURPOSE

To define and describe the accepted indications for Bosulif (bosutinib) usage in the treatment of cancer.

II. DEFINITIONS

Bosulif (bosutinib): is an oral tyrosine kinase inhibitor (TKI) that works by dual inhibition of the Bcr-Abl kinase that promotes chronic myelogenous leukemia (CML) and the Src-family of kinases (SFK) Src, Lyn, and Hck. In murine myeloid cell lines, bosutinib inhibited 16 of 18 imatinib-resistant forms of Bcr-Abl; T315I and V299L mutant cells were not inhibited. Bosutinib caused CML tumor cell reduction and myeloid tumor growth inhibition in several imatinib-resistant forms of Bcr-Abl in mice models. Bosutinib is 200-times more potent for the Bcr-Abl kinase than imatinib. SFK coordinate signaling from various transmembrane receptor-associated tyrosine kinases including epidermal growth factor receptor (EGFR), human epidermal growth factor receptor-2 (HER2), platelet derived growth factor receptor (PDGFR), and vascular endothelial growth factor receptor (VEGFR). Dysregulation and increased activity of Src occur in many malignancies and Src inhibitors have demonstrated activity in vitro in breast, colon, lung, pancreatic, and prostate tumors. Multidrug resistance (MDR) transporters promote the efflux of TKIs and upregulation of these transporters is one mechanism of resistance to TKIs. Bosutinib is not an efficient substrate for MDR transporters and may inhibit transport proteins at concentrations greater than 1 micromolar.

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

Non-FDA approved indication: Acute Lymphoblastic Leukemia (ALL).

Bosulif (bosutinib) is available in 100 mg, 400 mg and 500 mg tablets.

III. POLICY

New Century Health is responsible for processing all medication requests from network ordering providers. Medications not authorized by New Century Health may be deemed as not approvable and therefore not reimbursable.

Treatment request outside the approved FDA manufacturer labeling or CMS approved compendia must follow CMS Medicare Benefit Policy Manual Chapter 15. If references are not produced, delays may occur to the processing of such request.

Inclusion Criteria: Bosulif (bosutinib) may be considered medically necessary when any of the following selection criteria is met:

1. **Chronic Myelogenous Leukemia (CML)**
    a. The member has chronic, accelerated or blast phase of CML **AND** all of the following:

i. The member is Philadelphia chromosome or BCR-ABL positive **AND**

ii. The member has failed or is intolerant to prior therapy with Gleevec (imatinib) **AND** Tasigna (nilotinib) if Gleevec was used as first line therapy **OR**

iii. The member has failed or is intolerant to prior therapy with Tasigna (nilotinib) if used as first line therapy **AND**

iv. Failure is defined as ONE of the following:

A. BCR-ABL transcript levels greater than 10% at any response milestones **OR**

B. BCR-ABL1 transcript levels ≤10% but >1% at 12 months or ≥15 months

2. **Acute Lymphoblastic Leukemia (ALL)**

a. The member has ALL and Bosulif (bosutinib) is being used as therapy for relapsed/refractory Philadelphia chromosome-positive **ALL:**

i. As a single agent **OR**

ii. In combination with an induction regimen not previously given **OR**

iii. In patients with E255K/V, F317L/V/I/C, F359V/C/I, T315A, or Y253H mutations.

Exclusion Criteria: Bosulif (bosutinib) is not considered medically necessary when any of the following selection criteria is met:

1. Bosulif (bosutinib) is being used concurrently with Gleevec (imatinib), Sprycel (dasatinib), or Tasigna (nilotinib).
2. For CML: Contraindicated for use in patients with the following mutations: T315I, V299L, G250E, or F317L.
3. Dosing exceeds single dose limit of Bosulif (bosutinib) 600 mg.
4. Treatment exceeds the maximum duration limit of Bosulif (bosutinib) 30 (500 mg), 30 (400 mg), 30 (200 mg), or 30 (100 mg) capsules/month.
5. Indications not supported by CMS recognized compendia or acceptable peer reviewed literature may be deemed as not approvable and therefore not reimbursable.

IV. PROCEDURE

Requests for Bosulif (bosutinib) shall be reviewed for appropriateness per FDA approved product labeling, the National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) clinical guidelines, or CMS approved compendia.

1. **Dosage and Administration:**

a. Chronic, accelerated, or blast phase Ph+ CML with resistance or intolerance to prior therapy: 500 mg PO once daily with food until disease progression or drug intolerance.

b. Newly-diagnosed chronic phase Ph+ CML: 400 mg orally once daily with food.

c. The dosage may be increased to 600 mg PO once daily in patients who have not experienced grade 3 or higher toxicity and who have not achieved a complete hematological response (CHR) by week 8 or a complete cytogenic response (CCyR) by week 12.

2. **Dosage Adjustments:**

a. Diarrhea, grade 3 or 4: withhold until recovery to grade 1 or less; resume at 400 mg once daily.

b. Hepatic impairment, pre-existing mild, moderate, or severe: 200 mg ORALLY once daily.

c. Renal impairment, 30-50 ml/min: Reduce initial daily dose by 100 mg.

d. Renal impairment, less than 30 ml/min: Reduce initial daily dose by 200 mg.

e. Liver transaminases elevation: for elevations greater than 5 x ULN, withhold bosutinib until recovery to less than or equal to 2.5 x ULN and resume at 400 mg once daily, if recovery takes longer than 4 weeks, discontinue; for elevations greater than or equal to 3 x ULN with concurrent bilirubin elevation greater than 2 x ULN and alkaline phosphatase less than 2 x ULN, discontinue.

f. Myelosuppression: for an absolute neutrophil count (ANC) less than 1000 x 106/L OR platelets less than 50,000 X 106/L, stop bosutinib; when the ANC is at least 1000 x 106/L AND platelets are at least 50,000 x 106/L, resume at the same dose if recovery occurs within 2 weeks; if blood counts remain low for greater than 2 weeks, upon recovery, resume at a dose reduced by 100 mg; if cytopenia recurs, stop bosutinib until recovery and resume at a dose reduced by an additional 100 mg.

g. Non-hematological adverse events, moderate or severe: withhold until resolved and consider resuming at a dose that is 100 mg less than previous dose, and if clinically appropriate, consider escalating back to starting dose.

3. **Monitoring:**

a. Perform CBC with differential to measure hematologic response as an indication of efficacy.

b. Monitor cytogenetic response as an indication of efficacy.

c. Monitor hepatic enzymes monthly for the first 3 months of treatment and as clinically indicated; if transaminase levels elevate, monitor more frequently.

d. Renal function, paying close attention to patients with preexisting renal impairment or risk factors for renal dysfunction; at baseline and during therapy.

e. Perform CBC weekly for the first month of treatment and then monthly thereafter or as clinically indicated; include differential.

f. Monitor for signs of fluid retention, which may manifest as pericardial effusion, pleural effusion, pulmonary edema, or peripheral edema.

i. Signs of gastrointestinal toxicity, such as diarrhea, vomiting, and abdominal pain.

ii. Signs and symptoms of cardiac failure.

V. APPROVAL AUTHORITY

1. Review – Utilization Management Department
2. Final Approval – Utilization Management Committee

VI. ATTACHMENTS

None

VII. REFERENCES

1. Bosulif prescribing information. Pfizer Inc. 2019.
2. Clinical Pharmacology Elsevier Gold Standard. 2018.
3. Micromedex® Healthcare Series: Thomson Micromedex, Greenwood Village, Co. 2019.

4. National Comprehensive Cancer Network. Cancer Guidelines and Drugs and Biologics Compendium. 2019.