Bosulif® (bosutinib)
(Oral)

Document Number: IC-0021

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I. Length of Authorization

Coverage will be provided for 6 months and may be renewed, unless otherwise specified.

- CML: For patients with possible TKI-resistant disease, coverage will be provided for 3 months and may be renewed for 6 months if the treatment response milestone criteria for TKI-sensitive disease is achieved *(Refer to Section IV for specific response criteria)*

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

- Bosulif 100 mg tablets: 6 tablets per day
- Bosulif 400 mg tablets: 1 tablet per day
- Bosulif 500 mg tablets: 1 tablet per day
- Bosulif 50 mg capsules: 1 capsule per day
- Bosulif 100 mg capsules: 6 capsules per day

B. Max Units (per dose and over time) [HCPCS Unit]:

- 600 mg per day

III. Initial Approval Criteria [1]

Coverage is provided in the following conditions:

- Patient is at least 18 years of age, unless otherwise specified; **AND**

Universal Criteria [1]

- Patient will avoid concomitant therapy with all of the following:
  - Coadministration with strong CYP3A inducers (e.g., rifampin, carbamazepine, St. John's Wort, etc.); **AND**
  - Coadministration with moderate or strong CYP3A inhibitors (e.g., itraconazole, ketoconazole, fluconazole, ciprofloxacin, aprepitant, clarithromycin, etc.); **AND**

- Coadministration with proton pump inhibitors (e.g., lansoprazole, esomeprazole, omeprazole), or if acid-reduction therapy is required, short-acting antacids or H2 blockers may be used at staggered administration times; **AND**

Chronic Myelogenous Leukemia (CML) † Φ [1-3,6-8,11,12]

- Patient has Philadelphia chromosome-positive (Ph+) or *BCR::ABL1* positive disease; **AND**
- Patient does not have any of the following *BCR::ABL1* mutations: T315I, V299L, G250E, or F317L (****NOTE:** This does not apply to newly diagnosed chronic phase disease or continued therapy); **AND**
  - Patient is resistant, intolerant, or had an inadequate response to prior therapy consisting of a 3 month trial or longer with a tyrosine kinase inhibitor (e.g., imatinib, dasatinib, ponatinib, nilotinib, etc.) †; **AND**
    - Used as a single agent for chronic phase disease; **AND**
      - Patient is at least 1 year of age; **OR**
    - Used as a single agent for accelerated or blast phase disease; **OR**
  - Used post-allogeneic hematopoietic stem cell transplant (HCT) ‡; **AND**
    - Used as follow-up therapy in patients with molecular relapse (BCR::ABL1 transcript positive) following complete cytogenetic response (CCyR); **OR**
    - Used for at least one year in patients with prior CCyR for accelerated or blast phase disease; **OR**
    - Used as follow-up therapy in patients with relapse or less than CCyR; **OR**
  - Used as primary treatment † ‡; **AND**
    - Used as a single agent for newly diagnosed chronic phase disease; **AND**
      - Patient is at least 1 year of age; **OR**
    - Used as a single agent for accelerated phase disease; **OR**
    - Used as a single agent for myeloid blast phase disease if not a candidate for induction chemotherapy; **OR**
    - Used in combination with steroids for lymphoid blast phase disease if not a candidate for induction chemotherapy; **OR**
    - Used in combination with induction chemotherapy for disease in lymphoid blast phase or myeloid blast phase; **OR**
  - Used as switch therapy ‡; **AND**
    - Patient received primary treatment with one of the following: imatinib, dasatinib, or nilotinib; **AND**
    - Patient has *BCR::ABL1* transcript levels:
      - >0.1% to 1% at 12 months (if treatment goal is treatment-free remission); **OR**
      - >1% to 10% at 12 months; **OR**
      - >10% at any response milestone; **OR**
  - Used as continued therapy ‡; **AND**

- Patient has *BCR::ABL1* transcript levels:
  - ≤10% at any response milestone; **OR**
  - >10% at 3 months

Acute Lymphoblastic Leukemia (ALL) ‡ [2,4,5,10]

- Patient has Philadelphia chromosome-positive (Ph+) B-ALL; **AND**
- Patient does not have any of the following *BCR::ABL1* mutations: T315I, V299L, G250E, or F317L; **AND**
  - Used for relapsed or refractory disease; **AND**
    - Used as a single agent; **OR**
    - Used in combination inotuzumab ozogamicin; **OR**
    - Used in combination with blinatumomab; **OR**
  - Used as maintenance therapy; **AND**
    - Used in combination with POMP regimen (vincristine and prednisone with or without methotrexate and mercaptopurine); **AND**
      - Used following consolidation therapy for patients with negative minimal residual disease (if not already included in a multi-part regimen); **OR**
    - Used as single agent therapy; **AND**
      - Used post-hematopoietic stem cell transplant; **OR**
      - Used in patients unfit for additional therapies; **OR**
  - Used as induction therapy; **AND**
    - Used as frontline therapy OR for relapsed/refractory disease (if not previously given); **AND**
      - Used in combination with a corticosteroid; **OR**
      - Used in combination with vincristine and dexamethasone; **OR**
      - Used as a component of a multiagent chemotherapy regimen *(Note: May be used in patients at least 15 years of age)*; **OR**
  - Used as consolidation therapy; **AND**
    - Used for relapsed/refractory disease (if not previously given); **AND**
      - Used as a component of a multiagent chemotherapy regimen *(Note: May be used in patients at least 15 years of age)*; **OR**
    - Used as frontline therapy; **AND**
      - Used as a component of a multiagent chemotherapy regimen *(Note: May be used in patients at least 15 years of age)*; **OR**
      - Used as single agent therapy in patients unfit for additional therapies; **OR**
      - Used in combination with blinatumomab; **AND**
        - Used for persistent/rising minimal residual disease after complete response to induction therapy; **OR**

- Used for negative minimal residual disease after complete response to induction therapy if patient is not a candidate for multiagent therapy

Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes ‡ [2,9]

- Patient has eosinophilia and ABL1 rearrangement; **AND**
  - Patient has chronic or blast phase myeloid or lymphoid neoplasms; **AND**
    - Used as a single agent; **OR**
  - Patient has blast phase lymphoid, myeloid, or mixed lineage neoplasms; **AND**
    - Used in combination with ALL- or AML-type induction chemotherapy followed by allogeneic HCT (if eligible)

† FDA Approved Indication(s); ‡ Compendia Recommended Indication(s); Φ Orphan Drug

IV. Renewal Criteria [1-4,9]

Coverage can be renewed based upon the following criteria:

- Patient continues to meet universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in Section III; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: hepatic toxicity, renal toxicity, fluid retention (e.g., pericardial effusion, pleural effusion, pulmonary edema, and/or peripheral edema), myelosuppression (e.g., thrombocytopenia, anemia, neutropenia), gastrointestinal toxicity, cardiovascular toxicity (e.g., cardiac failure, left ventricular dysfunction, cardiac ischemic events), etc.; **AND**

Chronic Myelogenous Leukemia (CML)

- Treatment response as indicated by one of the following:
  - Patient has TKI-sensitive disease as confirmed by one of the following *BCR::ABL1* (IS) transcript levels:
    - ≤ 10% at 3 months or 6 months; **OR**
    - > 0.1% to 1% at 12 months and beyond (if treatment goal is long-term survival); **OR**
    - ≤ 0.1% at 12 months and beyond (if treatment goal is treatment-free remission); **OR**
  - Patient has <u>possible</u> TKI resistant disease as confirmed by a > 50% reduction in *BCR::ABL1* (IS) transcript levels compared to pretreatment baseline OR minimally above the 10% cutoff; **AND**
    - Treatment can be continued for an additional 3 months; **AND**
    - Follow-up *BCR::ABL1* (IS) transcript levels will be drawn after the 3 month extended treatment period to determine if continued treatment is warranted (i.e., patient meets the treatment response milestone criteria for TKI-sensitive disease as noted above)

Note: cytogenetic assessment of response may be used if quantitative RT-PCR (QPCR) using International Scale (IS) for *BCR::ABL1* is not available

Acute Lymphoblastic Leukemia (ALL)

- Treatment response or stabilization of disease as indicated by CBC, bone marrow cytogenic analysis, QPCR, or FISH

Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes

- Disease response as evidenced by at least one of the following:
  - Decrease in spleen size or improvements in other myelofibrosis symptoms (such as weakness, fatigue, cough, dyspnea, myalgias, angioedema, rash, fever, rhinitis, etc.)
  - Stabilization or improvement as evidenced by a complete response [CR] (i.e. morphologic, cytogenetic or molecular complete response CR), complete hematologic response, or a partial response by CBC, bone marrow cytogenic analysis, QPCR, or FISH

V. Dosage/Administration [1,3,5,9,10]

<table>
<tr><th>Indication</th><th>Dose</th></tr>
<tr><td>CML</td><td>
<u>Adults:</u>
• Newly diagnosed chronic phase Ph+ CML: Administer 400 mg orally once daily with food until disease progression or intolerance to therapy.
• All other treatment settings: Administer 500 mg orally once daily with food until disease progression or intolerance to therapy.
<u>Pediatrics:</u>
• Newly diagnosed, chronic phase Ph+ CML: Administer 300 mg/m^2 orally once daily with food until disease progression or intolerance to therapy. (See dose recommendations in table below)
• Chronic phase Ph+ CML with resistance, intolerance, or inadequate response to prior therapy: Administer 400 mg/m^2 orally once daily with food until disease progression or intolerance to therapy. (See dose recommendations in table below)
<table>
<tr><th>BSA</th><th>Newly Diagnosed</th><th>Resistant, Intolerant, or Inadequate Response</th></tr>
<tr><td>< 0.55 m^2</td><td>150 mg</td><td>200 mg</td></tr>
<tr><td>0.55 to < 0.63 m^2</td><td>200 mg</td><td>250 mg</td></tr>
<tr><td>0.63 to < 0.75 m^2</td><td>200 mg</td><td>300 mg</td></tr>
<tr><td>0.75 to < 0.9 m^2</td><td>250 mg</td><td>350 mg</td></tr>
</table>
</td></tr>
</table>

	<table><tr><td>0.9 to < 1.1 m^2</td><td>300 mg</td><td>400 mg</td></tr><tr><td>≥ 1.1 m^2</td><td>400 mg*</td><td>500 mg*</td></tr></table> **Maximum starting dose (corresponding to maximum starting dose in adult indication)* ***NOTE:*** *As appropriate, the desired dose can be attained by combining different strengths of tablets or capsules.*
ALL	Administer 500 mg orally once daily with food until disease progression or intolerance to therapy.
Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes	Administer 400 mg OR 500 mg orally once daily with food until disease progression or intolerance to therapy.
*****NOTE:*** • Consider dose escalation to 600 mg orally 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. • Swallow tablets whole. Capsules may be swallowed whole. For patients who are unable to swallow a whole capsule(s), each capsule can be opened and the contents mixed with applesauce or yogurt.	

VI. Billing Code/Availability Information

HCPCS Code:

- J8999 – Prescription drug, oral, chemotherapeutic, NOS

NDC:

- Bosulif 100 mg tablet: 00069-0135-xx
- Bosulif 400 mg tablet: 00069-0193-xx
- Bosulif 500 mg tablet: 00069-0136-xx
- Bosulif 50 mg capsules: 00069-0504-xx
- Bosulif 100 mg capsules: 00069-1014-xx

VII. References

1. Bosulif [package insert]. New York, NY; Pfizer, Inc; September 2023. Accessed October 2023.
2. Referenced with permission from the NCCN Drugs and Biologics Compendium (NCCN Compendium®) for bosutinib. National Comprehensive Cancer Network, 2023. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most

recent and complete version of the Compendium, go online to NCCN.org. Accessed August 2023.

3. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) for Chronic Myelogenous Leukemia 1.2024. National Comprehensive Cancer Network, 2023. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed August 2023.
4. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) for Acute Lymphoblastic Leukemia 1.2023. National Comprehensive Cancer Network, 2023. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed June 2023.
5. Gambacorti-Passerini C, Kantarjian HM, Kim DW, et al. Long-term efficacy and safety of bosutinib in patients with advanced leukemia following resistance/intolerance to imatinib and other tyrosine kinase inhibitors. Am J Hematol. 2015 Sep;90(9):755-68.
6. Cortes JE, Gambacorti-Passerini C, Deininger MW, et al. Bosutinib Versus Imatinib for Newly Diagnosed Chronic Myeloid Leukemia: Results From the Randomized BFORE Trial. J Clin Oncol. 2018 Jan 20;36(3):231-237. doi: 10.1200/JCO.2017.74.7162.
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9. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes. Version 1.2023. National Comprehensive Cancer Network, 2023. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed June 2023.
10. Kantarjian HM, Cortes JE, Kim DW, et al. Bosutinib safety and management of toxicity in leukemia patients with resistance or intolerance to imatinib and other tyrosine kinase inhibitors. Blood. 2014 Feb 27;123(9):1309-18. doi: 10.1182/blood-2013-07-513937. Epub 2013 Dec 17. Erratum in: Blood. 2014 Aug 7;124(6):981.

11. Pennesi E, Brivio E, Willemse ME, et al. Preliminary results from the first-in-child phase II trial (ITCC-054/COG-AAML1921) of bosutinib in pediatric patients with newly diagnosed (ND) chronic myeloid leukemia (CML). Journal of Clinical Oncology 2023 41:16_suppl, 10017-10017. DOI: 10.1200/JCO.2023.41.16_suppl.10017.
12. Pennesi E, Brivio E, Willemse ME, et al. A Phase I/II Study of Bosutinib in Pediatric Patients with Resistant/Intolerant or Newly Diagnosed Philadelphia Chromosome-Positive Chronic Myeloid Leukemia, Study ITCC (Innovative Therapies for Children with Cancer European Consortium) 054 and COG (Children's Oncology Group Consortium) AAML1921: Results from the Phase I Trial in Resistant/Intolerant Patients. Blood, Volume 138, Supplement 1, 2021, Page 2558, ISSN 0006-4971. https://doi.org/10.1182/blood-2021-145709.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C83.50	Lymphoblastic (diffuse) lymphoma, unspecified site
C83.51	Lymphoblastic (diffuse) lymphoma, lymph nodes of head, face, and neck
C83.52	Lymphoblastic (diffuse) lymphoma, intrathoracic lymph nodes
C83.53	Lymphoblastic (diffuse) lymphoma, intra-abdominal lymph nodes
C83.54	Lymphoblastic (diffuse) lymphoma, lymph nodes of axilla and upper limb
C83.55	Lymphoblastic (diffuse) lymphoma, lymph nodes of inguinal region and lower limb
C83.56	Lymphoblastic (diffuse) lymphoma, intrapelvic lymph nodes
C83.57	Lymphoblastic (diffuse) lymphoma, spleen
C83.58	Lymphoblastic (diffuse) lymphoma, lymph nodes of multiple sites
C83.59	Lymphoblastic (diffuse) lymphoma, extranodal and solid organ sites
C91.00	Acute lymphoblastic leukemia not having achieved remission
C91.01	Acute lymphoblastic leukemia, in remission
C91.02	Acute lymphoblastic leukemia, in relapse
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
C94.8	Other specified leukemias
C94.80	Other specified leukemias not having achieved remission
C94.81	Other specified leukemias, in remission
C94.82	Other specified leukemias, in relapse
C95.1	Chronic leukemia of unspecified cell type
C95.10	Chronic leukemia of unspecified cell type not having achieved remission
C95.11	Chronic leukemia of unspecified cell type, in remission

C95.12	Chronic leukemia of unspecified cell type, in relapse
C96.Z	Other specified malignant neoplasms of lymphoid, hematopoietic and related tissue
C96.9	Malignant neoplasm of lymphoid, hematopoietic and related tissue, unspecified

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determination (NCD), Local Coverage Determinations (LCDs), and Local Coverage Articles (LCAs) may exist and compliance with these policies is required where applicable. They can be found at: https://www.cms.gov/medicare-coverage-database/search.aspx. Additional indications may be covered at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA): N/A

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC