Imbruvica® (ibrutinib)
(Oral)

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I. Length of Authorization

Coverage will be provided for 6 months and may be renewed.

II. Dosing Limits

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

- Imbruvica 70 mg capsule: 1 capsule per day
- Imbruvica 70 mg/mL oral suspension: 6 mL (420 mg) per day
- Imbruvica 140 mg capsule/tablet: 4 capsules/tablets per day
- Imbruvica 280 mg tablet: 2 tablets per day
- Imbruvica 420 mg tablet: 2 tablets per day
- Imbruvica 560 mg tablet: 1 tablet per day

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

cGVHD, CLL/SLL, WM/LPL, Hairy Cell Leukemia
- 420 mg daily

B-Cell Lymphomas
- 560 mg daily

Central Nervous System (CNS) Cancers
- 840 mg daily

III. Initial Approval Criteria [1]

Coverage for is provided for treatment of 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 voriconazole, posaconazole, and moderate CYP3A inhibitors (e.g., aprepitant, ciprofloxacin, diltiazem, erythromycin, etc.), or if therapy is

unavoidable, the patient will be monitored closely for adverse reaction and/or dose modifications will be implemented; **AND**

- Coadministration with other strong CYP3A inhibitors (e.g., clarithromycin, ketoconazole, nefazodone, grapefruit, Seville oranges, etc.); **AND**
- Coadministration with strong CYP3A inducers (e.g., rifampin, carbamazepine, St. John's Wort, etc.); **AND**

- Patient does not have severe hepatic impairment (Child-Pugh class C); **AND**

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) † ‡ Φ [1,2,29]

- Used as a single agent

Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma (WM/LPL) † Φ [1,2,27]

- Used as single agent or in combination with rituximab; **OR**
- Patient has symptomatic Bing-Neel syndrome; **AND**
  - Used as a single agent or in combination with rituximab if systemic control is needed

Chronic Graft versus Host Disease (cGVHD) † Φ [1,2]

- Patient is at least 1 year of age; **AND**
- Used as a single agent or in conjunction with systemic steroids; **AND**
- Patient is post-allogeneic stem cell transplant (generally 3 or more months); **AND**
- Patient has failed one or more previous lines of systemic therapy for the treatment of cGVHD (e.g., corticosteroids or immunosuppressants such as cyclosporine)

B-Cell Lymphomas ‡ [1-3]

- Diffuse Large B-Cell Lymphoma (DLBCL), High Grade B-Cell Lymphomas, and HIV-Related B-Cell Lymphomas
  - Used as a single agent as subsequent therapy if no intention to proceed to transplant for patients with non-germinal center disease; **AND**
    - Used for relapsed or refractory disease >12 months after completion of first-line therapy; **OR**
    - Used for primary refractory disease (partial response, no response, or progression) or relapsed disease <12 months after completion of first-line therapy*****; **OR**
    - Used as alternative systemic therapy (if not previously used) for relapsed/refractory disease*****
- Monomorphic Post-Transplant Lymphoproliferative Disorders (PTLD)
  - Used as a single agent as subsequent therapy for non-germinal center B-cell type disease; **AND**
    - Used for relapsed or refractory disease >12 months after completion of initial treatment with chemoimmunotherapy; **OR**

        - Used for primary refractory disease (partial response, no response, or progression) or relapsed disease <12 months after completion of initial treatment with chemoimmunotherapy*; **OR**
        - Used as alternative systemic therapy (if not previously used) for relapsed/refractory disease*; **OR**
- Extranodal Marginal Zone Lymphoma (of Nongastric Sites [Non-cutaneous] or of the Stomach) or Marginal Zone Lymphoma (Splenic or Nodal)
    - Used as a single agent as subsequent therapy; **AND**
    - Used for relapsed, refractory, or progressive disease
- Mantle Cell Lymphoma (MCL)
    - Used as aggressive induction therapy; **AND**
        - Used as a component of TRIANGLE regimen: alternating RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) + covalent Bruton tyrosine kinase inhibitor (ibrutinib)/RDHAP (rituximab, dexamethasone, and cytarabine) + carboplatin regimen; **AND**
            - Used as additional therapy for stage I-II disease following partial response, progression, or relapse after initial treatment with involved site radiation therapy alone; **OR**
            - Used as re-induction therapy, in selected cases, for relapse after initial treatment with chemoimmunotherapy; **OR**
            - Used for classical or indolent TP53 wildtype stage II bulky or noncontiguous, III, or IV disease; **OR**
            - Used for classical or indolent TP53 mutated stage II bulky or noncontiguous, III, or IV disease in the absence of a clinical trial; **OR**
    - Used as subsequent therapy as a single agent OR in combination with rituximab or venetoclax; **AND**
        - Used for stage I-II disease with partial response, relapse, or progression after prior treatment with chemoimmunotherapy; **OR**
        - Used for classical or indolent stage II bulky or noncontiguous, III, or IV disease in patients who have stable or progressive disease or partial response with substantial disease after induction therapy; **OR**
        - Used for relapsed or refractory disease (if not previously given); **OR**
    - Used in combination with rituximab as pre-treatment to limit the number of aggressive induction therapy cycles with RHyperCVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone) regimen; **OR**
    - Used as maintenance therapy; **AND**
        - Used in combination with rituximab; **AND**
            - Used following high dose therapy/autologous stem cell rescue; **OR**

- Used for complete response following aggressive induction therapy (i.e., alternating RCHOP + ibrutinib/RDHAP)

**Note: Only applies to patients in which there is no intention to proceed to CAR T-cell therapy.*

Central Nervous System (CNS) Cancers ‡ [2,16,23]

- Used for the treatment of brain metastases in patients with lymphoma; **AND**
  - Used as initial treatment in patients with small asymptomatic brain metastases; **OR**
  - Patient has recurrent limited brain metastases; **OR**
  - Used for relapsed disease limited brain metastases and either stable systemic disease or reasonable systemic treatment options; **OR**
  - Used for recurrent extensive brain metastases and stable systemic disease or reasonable systemic treatment options; **OR**
- Patient has primary CNS lymphoma; **AND**
  - Used for relapsed or refractory disease**; AND**
    - Used as a single agent; **AND**
      - Patient has received previous whole brain radiation therapy; **OR**
      - Patient has received previous treatment with a high-dose methotrexate-based regimen without prior radiation therapy; **OR**
      - Used in combination with radiation therapy in patients who had either no response or a short response (< 12 month duration) to a high-dose methotrexate-based regimen without previous radiation therapy; **OR**
      - Patient has received previous high-dose systemic therapy with stem cell rescue; **OR**
    - Used in combination with high-dose methotrexate and rituximab; **AND**
      - Patient has received previous whole brain radiation therapy; **OR**
      - Patient has received previous treatment with a high-dose methotrexate-based regimen without prior radiation therapy; **OR**
  - Used as induction therapy as a single agent; **AND**
    - Patient is unsuitable for or intolerant to high-dose methotrexate

Hairy Cell Leukemia ‡ [2,24]

- Used as a single agent for progression after therapy for relapsed/refractory disease

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

IV. Renewal Criteria [1]

Coverage can be renewed based on the following criteria:

- Patient continues to meet the universal and other indication-specific relevant criteria identified in section III; **AND**

- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: hemorrhage, severe infections, cytopenias (neutropenia, thrombocytopenia, anemia), cardiac arrhythmias (ventricular tachyarrhythmia, atrial fibrillation/flutter), cardiac failure, tumor lysis syndrome, uncontrolled hypertension, second primary malignancies, etc.; **AND**

Oncology indications:

- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread

cGVHD:

- Response to therapy with an improvement in one or more of the following:
  - Clinician assessments (e.g., NIH Skin Score, Upper GI Response Score, NIH Lung Symptom Score, etc.)
  - Patient-reported symptoms (e.g., Lee Symptom Scale, etc.)

V. Dosage/Administration [1,3,7,21-23,25]

<table>
<tr><th>Indication</th><th>Dose</th></tr>
<tr><td>B-Cell Lymphomas</td><td>560 mg orally once daily until disease progression or unacceptable toxicity</td></tr>
<tr><td>CLL/SLL</td><td>420 mg orally once daily until disease progression or unacceptable toxicity</td></tr>
<tr><td>WM/LPL (single agent or in combination with rituximab)</td><td>420 mg orally once daily until disease progression or unacceptable toxicity</td></tr>
<tr><td>cGVHD</td><td>

≥ 12 years of age: 420 mg orally once daily until progression, recurrence of an underlying malignancy, or unacceptable toxicity
≥ 1 year of age to < 12 years of age: 240 mg/m2 orally once daily (up to a dose of 420 mg), until progression, recurrence of an underlying malignancy, or unacceptable toxicity (refer to dosing table below)

<table>
<tr><th>BSA (m^2) Range</th><th>Dose (mg)
Capsules or Tablets</th><th>Volume (mL)
Oral Suspension (70 mg/mL)</th></tr>
<tr><td>> 0.3 to 0.4</td><td>N/A</td><td>1.2 mL</td></tr>
<tr><td>> 0.4 to 0.5</td><td>N/A</td><td>1.5 mL</td></tr>
<tr><td>> 0.5 to 0.6</td><td>N/A</td><td>1.9 mL</td></tr>
<tr><td>> 0.6 to 0.7</td><td>N/A</td><td>2.2 mL</td></tr>
<tr><td>> 0.7 to 0.8</td><td>210 mg</td><td>2.6 mL</td></tr>
<tr><td>> 0.8 to 0.9</td><td>210 mg</td><td>2.9 mL</td></tr>
<tr><td>> 0.9 to 1.0</td><td>210 mg</td><td>3.3 mL</td></tr>
<tr><td>> 1.0 to 1.1</td><td>280 mg</td><td>3.6 mL</td></tr>
<tr><td>> 1.1 to 1.2</td><td>280 mg</td><td>4 mL</td></tr>
<tr><td>> 1.2 to 1.3</td><td>280 mg</td><td>4.3 mL</td></tr>
</table>
</td></tr>
</table>

Indication	Dose		
	> 1.3 to 1.4	350 mg	4.6 mL
	> 1.4 to 1.5	350 mg	5 mL
	> 1.5 to 1.6	350 mg	5.3 mL
	> 1.6	420 mg	6 mL
Central Nervous System (CNS) Cancers	**Primary CNS Lymphoma** 560 or 840 mg orally once daily until disease progression or unacceptable toxicity **Brain metastases in patients with lymphoma** 560 mg orally once daily until disease progression or unacceptable toxicity		
Hairy Cell Leukemia	420 mg once daily until disease progression or unacceptable toxicity		

VI. Billing Code/Availability Information

HCPCS Code:

- J8999 — Prescription drug, oral, chemotherapeutic, Not Otherwise Specified

NDC:

- Imbruvica 70 mg capsule: 57962-0070-xx
- Imbruvica 70 mg/mL oral suspension: 57962-0007-xx
- Imbruvica 140 mg capsule: 57962-0140-xx
- Imbruvica 140 mg tablet: 57962-0014-xx
- Imbruvica 280 mg tablet: 57962-0280-xx
- Imbruvica 420 mg tablet: 57962-0420-xx
- Imbruvica 560 mg tablet: 57962-0560-x

VII. References

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2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) for ibrutinib. 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 September 2023.
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29. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma. Version 3.2023. 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 October 2023.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C79.31	Secondary malignant neoplasm of brain
C81.09	Nodular lymphocyte predominant Hodgkin lymphoma, extranodal and solid organ sites
C81.19	Nodular sclerosis Hodgkin lymphoma, extranodal and solid organ sites
C81.29	Mixed cellularity Hodgkin lymphoma, extranodal and solid organ sites
C81.39	Lymphocyte depleted Hodgkin lymphoma, extranodal and solid organ sites
C81.49	Lymphocyte-rich Hodgkin lymphoma, extranodal and solid organ sites
C81.79	Other Hodgkin lymphoma, extranodal and solid organ sites
C81.99	Hodgkin lymphoma, unspecified, extranodal and solid organ sites
C82.09	Follicular lymphoma grade I, extranodal and solid organ sites
C82.19	Follicular lymphoma grade II, extranodal and solid organ sites

ICD-10	ICD-10 Description
C82.29	Follicular lymphoma grade III, unspecified, extranodal and solid organ sites
C82.39	Follicular lymphoma grade IIIa, extranodal and solid organ sites
C82.49	Follicular lymphoma grade IIIb, extranodal and solid organ sites
C82.59	Diffuse follicle center lymphoma, extranodal and solid organ sites
C82.69	Cutaneous follicle center lymphoma, extranodal and solid organ sites
C82.89	Other types of follicular lymphoma, extranodal and solid organ sites
C82.99	Follicular lymphoma, unspecified, extranodal and solid organ sites
C83.00	Small cell B-cell lymphoma, unspecified site
C83.01	Small cell B-cell lymphoma, lymph nodes of head, face, and neck
C83.02	Small cell B-cell lymphoma, intrathoracic lymph nodes
C83.03	Small cell B-cell lymphoma, intra-abdominal lymph nodes
C83.04	Small cell B-cell lymphoma, lymph nodes of axilla and upper limb
C83.05	Small cell B-cell lymphoma, lymph nodes of inguinal region and lower limb
C83.06	Small cell B-cell lymphoma, intrapelvic lymph nodes
C83.07	Small cell B-cell lymphoma, spleen
C83.08	Small cell B-cell lymphoma, lymph nodes of multiple sites
C83.09	Small cell B-cell lymphoma, extranodal and solid organ sites
C83.10	Mantle cell lymphoma, unspecified site
C83.11	Mantle cell lymphoma, lymph nodes of head, face, and neck
C83.12	Mantle cell lymphoma, intrathoracic lymph nodes
C83.13	Mantle cell lymphoma, intra-abdominal lymph nodes
C83.14	Mantle cell lymphoma, lymph nodes of axilla and upper limb
C83.15	Mantle cell lymphoma, lymph nodes of inguinal region and lower limb
C83.16	Mantle cell lymphoma, intrapelvic lymph nodes
C83.17	Mantle cell lymphoma, spleen
C83.18	Mantle cell lymphoma, lymph nodes of multiple sites
C83.19	Mantle cell lymphoma, extranodal and solid organ sites
C83.30	Diffuse large B-cell lymphoma, unspecified site
C83.31	Diffuse large B-cell lymphoma, lymph nodes of head, face, and neck
C83.32	Diffuse large B-cell lymphoma, intrathoracic lymph nodes
C83.33	Diffuse large B-cell lymphoma, intra-abdominal lymph nodes
C83.34	Diffuse large B-cell lymphoma, lymph nodes of axilla and upper limb
C83.35	Diffuse large B-cell lymphoma, lymph nodes of inguinal region and lower limb
C83.36	Diffuse large B-cell lymphoma, intrapelvic lymph nodes
C83.37	Diffuse large B-cell lymphoma, spleen
C83.38	Diffuse large B-cell lymphoma, lymph nodes of multiple sites

ICD-10	ICD-10 Description
C83.39	Diffuse large B-cell lymphoma, extranodal and solid organ sites
C83.59	Lymphoblastic (diffuse) lymphoma, extranodal and solid organ sites
C83.79	Burkitt lymphoma, extranodal and solid organ sites
C83.80	Other non-follicular lymphoma, unspecified site
C83.81	Other non-follicular lymphoma, lymph nodes of head, face and neck
C83.82	Other non-follicular lymphoma, intrathoracic lymph nodes
C83.83	Other non-follicular lymphoma, intra-abdominal lymph nodes
C83.84	Other non-follicular lymphoma, lymph nodes of axilla and upper limb
C83.85	Other non-follicular lymphoma, lymph nodes of inguinal region and lower limb
C83.86	Other non-follicular lymphoma, intrapelvic lymph nodes
C83.87	Other non-follicular lymphoma, spleen
C83.88	Other non-follicular lymphoma, lymph nodes of multiple sites
C83.89	Other non-follicular lymphoma, extranodal and solid organ sites
C83.90	Non-follicular (diffuse) lymphoma, unspecified, unspecified site
C83.91	Non-follicular (diffuse) lymphoma, unspecified, lymph nodes of head, face, and neck
C83.92	Non-follicular (diffuse) lymphoma, unspecified, intrathoracic lymph nodes
C83.93	Non-follicular (diffuse) lymphoma, unspecified, intra-abdominal lymph nodes
C83.94	Non-follicular (diffuse) lymphoma, unspecified, lymph nodes of axilla and upper limb
C83.95	Non-follicular (diffuse) lymphoma, unspecified, lymph nodes of inguinal region and lower limb
C83.96	Non-follicular (diffuse) lymphoma, unspecified, intrapelvic lymph nodes
C83.97	Non-follicular (diffuse) lymphoma, unspecified, spleen
C83.98	Non-follicular (diffuse) lymphoma, unspecified, lymph nodes of multiple sites
C83.99	Non-follicular (diffuse) lymphoma, unspecified, extranodal and solid organ sites
C84.09	Mycosis fungoides, extranodal and solid organ sites
C84.19	Sézary disease, extranodal and solid organ sites
C84.49	Peripheral T-cell lymphoma, not elsewhere classified, extranodal and solid organ sites
C84.69	Anaplastic large cell lymphoma, ALK-positive, extranodal and solid organ sites
C84.79	Anaplastic large cell lymphoma, ALK-negative, extranodal and solid organ sites
C84.A9	Cutaneous T-cell lymphoma, unspecified, extranodal and solid organ sites
C84.Z9	Other mature T/NK-cell lymphomas, extranodal and solid organ sites
C84.99	Mature T/NK-cell lymphomas, unspecified, extranodal and solid organ sites
C85.10	Unspecified B-cell lymphoma, unspecified site
C85.11	Unspecified B-cell lymphoma, lymph nodes of head, face, and neck
C85.12	Unspecified B-cell lymphoma, intrathoracic lymph nodes
C85.13	Unspecified B-cell lymphoma, intra-abdominal lymph nodes
C85.14	Unspecified B-cell lymphoma, lymph nodes of axilla and upper limb

ICD-10	ICD-10 Description
C85.15	Unspecified B-cell lymphoma, lymph nodes of inguinal region and lower limb
C85.16	Unspecified B-cell lymphoma, intrapelvic lymph nodes
C85.17	Unspecified B-cell lymphoma, spleen
C85.18	Unspecified B-cell lymphoma, lymph nodes of multiple sites
C85.19	Unspecified B-cell lymphoma, extranodal and solid organ sites
C85.29	Mediastinal (thymic) large B-cell lymphoma, extranodal and solid organ sites
C85.80	Other specified types of non-Hodgkin lymphoma, unspecified site
C85.81	Other specified types of non-Hodgkin lymphoma, lymph nodes of head, face and neck
C85.82	Other specified types of non-Hodgkin lymphoma, intrathoracic lymph nodes
C85.83	Other specified types of non-Hodgkin lymphoma, intra-abdominal lymph nodes
C85.84	Other specified types of non-Hodgkin lymphoma, lymph nodes of axilla and upper limb
C85.85	Other specified types of non-Hodgkin lymphoma, lymph nodes of inguinal region of lower limb
C85.86	Other specified types of non-Hodgkin lymphoma, intrapelvic lymph nodes
C85.87	Other specified types of non-Hodgkin lymphoma, spleen
C85.88	Other specified types of non-Hodgkin lymphoma, lymph nodes of multiple sites
C85.89	Other specified types of non-Hodgkin lymphoma, extranodal and solid organ sites
C85.99	Non-Hodgkin lymphoma, unspecified, extranodal and solid organ sites
C88.0	Waldenström macroglobulinemia
C88.4	Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT-lymphoma)
C91.10	Chronic lymphocytic leukemia of B-cell type not having achieved remission
C91.12	Chronic lymphocytic leukemia of B-cell type in relapse
C91.40	Hairy cell leukemia not having achieved remission
C91.42	Hairy cell leukemia, in relapse
D47.Z1	Post-transplant lymphoproliferative disorder (PTLD)
D89.811	Chronic graft-versus-host disease
D89.812	Acute on chronic graft-versus-host disease
D89.813	Graft-versus-host disease, unspecified
T86.09	Other complications of bone marrow transplant
Z85.71	Personal history of Hodgkin lymphoma
Z85.72	Personal history of non-Hodgkin lymphomas
Z85.79	Personal history of other malignant neoplasms of lymphoid, hematopoietic and related tissues

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 Article (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