CLINICAL GUIDELINES FOR MEDICAL NECESSITY

MEDICAL POLICY

Ibrutinib (Imbruvica®)

Version: 1.0

EFFECTIVE DATE: 12/1/2024

NantHealth® | Eviti®

Please note the following:

Ibrutinib (Imbruvica®)

Note: For Medicare members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Please refer to the CMS website at http://www.cms.gov for additional information.

Note: For Medicaid members/enrollees, circumstances when state Medicaid coverage provisions conflict with the coverage provisions within this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Ibrutinib (Imbruvica): Discussion

Ibrutinib is a small-molecule inhibitor of Bruton's tyrosine kinase (BTK). Ibrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. BTK's role in signaling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis, and adhesion.[1]

Abnormal BCR signaling is a key mechanism of disease progression in B-cell malignancy. BTK has a pivotal role in BCR signaling. Ibrutinib is a novel agent which serves as a covalent irreversible inhibitor of BTK. It is characterized by high selectivity for BTK and high potency.[2]

The most common adverse reactions associated with ibrutninib are hemorrhage, infections, cardiac arrhythmias, cardiac failure, sudden death, hypertension, cytopenias, secondary primary malignancies, hepatotoxicity including drug-induced liver injury, and tumor lysis syndrome.

Ibrutinib is approved by the Food and Drug Administration (FDA) for chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma, Waldenström's macroglobulinemia and chronic graft versus host disease.[1]

The National Comprehensive Cancer Network (NCCN) endorses ibrutinib in the following cancer types:, hairy cell leukemia, chronic lymphocytic leukemia/small lymphocytic lymphoma, primary CNS lymphoma, limited brain metastases, extensive brain metastases, extranodal marginal zone lymphoma of the stomach and non-gastric sites (noncutaneous), nodal marginal zone lymphoma, splenic marginal zone lymphoma, mantle cell lymphoma, diffuse large b-cell lymphoma, high-grade b-cell lymphomas, HIV-related B-cell lymphomas, post-transplant lymphoproliferative disorders, hematopoietic cell transplantation, and Waldenström macroglobulinemia/lymphoplasmacytic lymphoma.[3,4,5,6,7,8]

Ibrutinib: Definitions

- **National Comprehensive Cancer Network (NCCN)** - An alliance of more than 30 leading cancer centers devoted to patient care, research, and education. The NCCN guidelines are utilized for Radiation Therapy and Medical Oncology standards. NCCN

consensus clinical standards are periodically updated and NantHealth, Inc. reviews these and updates its policies within a timely manner.

- **Food and Drug Administration (FDA)** - The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.
- **Bruton's tyrosine kinase (BTK)** - A tyrosine-protein kinase (TEC) that plays a critical role in B-cell biology and function and is a component of the B-cell receptor signaling pathway. This is significant in various immune system pathways and cells beyond B cells, including T cells and macrophages.[9]

Ibrutinib: Policy

Note: Coverage of ibrutinib will be provided for an FDA-approved indication or National Comprehensive Cancer Network (NCCN) guidelines when it is a Category 1, 2A, or 2B recommendation or when all criteria are met.

Ibrutinib will be considered for coverage when the following criteria are met:

Hematopoietic Cell Transplantation

1. At least 1 years of age and older; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

3. Chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy[1]; OR

For **NCCN** required criteria coverage:

4. cGVHD as additional therapy in conjunction with systemic corticosteroids following no response (steroid refractory disease) to first-line therapy options.[3]

Hairy Cell Leukemia

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Single agent in patients with indications for treatment for progression after therapy for relapsed/refractory disease.[4]

Chronic Lymphocytic Leukemia And Small Lymphocytic Lymphoma

1. At least 18 years of age; AND

2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

3. With or without 17p deletion[1]; OR

For **NCCN** required criteria coverage:

4. Covalent Bruton Tyrosine Kinase Inhibitor (cBTKi) used as first-line therapy for CLL/SLL without del(17p)/TP53 mutation in patients who have indications for treatment for one of the following:
   a) Single agent
   b) In combination with anti-CD20 mAb (obinutuzumab or rituximab); OR
5. cBTKi used in combination with venetoclax for CLL/SLL with or without del(17p)/TP53 mutation in patients who have indications for treatment for one of the following:
   a) First-line therapy
   b) Second-line or subsequent therapy
   c) Relapsed or refractory disease after prior Bruton Tyrosine Kinase inhibitor and venetoclax-based regimens; OR
6. Second-line or subsequent therapy as a single agent for CLL/SLL without del(17p)/TP53 mutation in patients who have indications for treatment for one of the following:
   a) Alternate to cBTKi for patients who develop intolerance to a cBTKi given with or without obinutuzumab as first-line therapy
   b) Alternate to cBTKi, not given as first-line therapy, following second-line therapy with venetoclax with or without anti-CD20 monoclonal antibody (mAb)
   c) Relapse after first-line therapy with fixed-duration treatment (venetoclax and obinutuzumab, chemoimmunotherapy, or immunotherapy)
   d) Progression or intolerance while on first-line therapy with fixed duration treatment (venetoclax and obinutuzumab, chemoimmunotherapy, or immunotherapy)
   e) Third-line therapy for disease relapse following treatment with venetoclax with or without anti-CD20 mAb if fixed duration treatment (venetoclax and obinutuzumab, chemoimmunotherapy, or immunotherapy) was given as first-line therapy; OR

Note: Alternate cBTKi (acalabrutinib or zanubrutinib) for intolerance in the absence of disease progression.

7. cBTKi used in combination with nivolumab or pembrolizumab for histologic (Richter) transformation to diffuse large B-cell lymphoma (clonally related or unknown clonal status) in patients with del(17p)/TP53 mutation or who are chemotherapy refractory or unable to receive chemoimmunotherapy.

Central Nervous System Cancers

Primary CNS Lymphoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Induction therapy as a single agent if the patient is unsuitable for or intolerant to high dose methotrexate; OR
4. Single agent for relapsed or refractory disease for one of the following:
   a) Prior whole brain radiation therapy
   b) Prior high-dose methotrexate-based regimen without prior radiation therapy (RT)
   c) In combination with whole brain RT or involved field RT in patients who received a prior high dose methotrexate-based regimen without prior RT after no response or short response duration (<12 months) to prior regimen
   d) Prior high dose systemic therapy with stem cell rescue; OR
5. Treatment in combination with high-dose methotrexate and rituximab for relapsed or refractory disease for one of the following:
   a) Prior whole brain RT
   b) Prior high dose methotrexate-based regimen without prior radiation therapy (RT) after previous long response duration (≥12 months) to prior regimen
   c) Prior high dose methotrexate-based regimen without prior RT after previous short response duration (<12 months) to prior regimen if clinically indicated.

Limited Brain Metastases

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Single agent treatment in lymphoma for one of the following:
   a) Initial treatment in select cases (small asymptomatic brain metastases)
   b) Recurrent brain metastases
   c) Relapsed disease with either stable systemic disease or reasonable systemic treatment options.

Extensive Brain Metastases

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Single agent treatment in lymphoma for one of the following:
   a) Primary treatment in select cases (small asymptomatic brain metastases)
   b) Recurrent disease with stable systemic disease or reasonable systemic treatment options.[6]

B-Cell Lymphomas

Extranodal Marginal Zone Lymphoma of the Stomach/ Non-gastric Sites (Noncutaneous)/Nodal/Splenic Marginal Zone Lymphoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Subsequent therapy for relapsed, refractory, or progressive disease in patients with indications for treatment, including for older or infirm patients when tolerability of combination chemoimmunotherapy is a concern.

Mantle Cell Lymphoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Aggressive induction therapy 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, cisplatin, or oxaliplatin) regimen for one of the following:
   a) Stage I-II disease following partial response, progression, or relapse after initial treatment with involved site radiation therapy alone
   b) Re-induction therapy for stage I-II disease, in selected cases, for relapse after initial treatment with chemoimmunotherapy
   c) Classical or indolent TP53 wildtype stage II bulky noncontiguous or stage III, IV disease; OR

Note: Alternate covalent BTKi (acalabrutinib) was not evaluated in the Triangle study

4. Aggressive induction therapy for classical or indolent TP53 mutated stage II bulky noncontiguous or stage III, IV disease as a component of Triangle regimen: alternating RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) plus covalent bruton tyrosine kinase inhibitor (ibrutinib)/RDHA (rituximab, dexamethasone, and cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin) regimen; OR

Note: TP53 mutation has been associated with a poor prognosis in patients treated with conventional therapy, including transplant.

5. In combination with rituximab as pre-treatment in order to limit the number of cycles of aggressive induction therapy with RHyperCVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone) regimen; OR
6. In combination with rituximab as maintenance therapy for one of the following:
   a) Complete response following aggressive induction therapy
   b) Following high dose therapy and autologous stem cell rescue; OR

7. Second-line and subsequent therapy, or as a single agent or in combination with rituximab, or in combination with venetoclax for one of the following:
   a) Stage I-II disease with partial response, relapse, or progression after prior treatment with chemoimmunotherapy
   b) Classical or indolent TP53 wildtype stage II bulky or noncontiguous or stage III, IV disease in patients who have no response or progressive disease or partial response with substantial disease after induction therapy
   c) Relapsed or refractory disease

Diffuse Large B-Cell Lymphoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Single agent as second-line and subsequent therapy if no intention to proceed to transplant with non-germinal center diffuse large B-cell lymphoma for one of the following:
   a) Relapsed disease >12 months after completion of first-line therapy
   b) Primary refractory disease (partial response, no response, or progression) or relapsed disease <12 months after completion of first-line therapy for in non-candidates for CAR T-cell therapy
   c) Alternative systemic therapy (if not previously used) for relapsed/refractory disease in non-candidates for CAR T-cell therapy.

High-Grade B-Cell Lymphomas

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Single agent as subsequent therapy if no intention to proceed to transplant with non-germinal center diffuse large B-cell lymphoma for one of the following:
   a) Relapsed disease >12 months after completion of first-line therapy
   b) Primary refractory disease (partial response, no response, or progression) or relapsed disease <12 months after completion of first-line therapy in non-candidates for CAR T-cell therapy
   c) Alternative systemic therapy for relapsed/refractory disease in non-candidates for CAR T-cell therapy.

HIV-Related B-Cell Lymphomas

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Second-line and subsequent therapy as a single agent for HIV-related non-germinal center diffuse large B-cell lymphoma if no intention to proceed to transplant for one of the following:
   a) Relapsed disease >12 months after completion of first-line therapy
   b) Primary refractory disease (partial response, no response, or progression) or relapsed disease <12 months after completion of first-line therapy in non-candidates for CAR T-cell therapy
   c) Alternative systemic therapy (if not previously used) for relapsed/refractory disease in non-candidates for CAR T-cell therapy.

Post-Transplant Lymphoproliferative Disorders

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Second-line and subsequent therapy as a single agent for monomorphic PTLD (non-germinal center B-cell type) if no intention to proceed to transplant for one of the following:
   a) Relapsed disease >12 months after completion of initial treatment with chemoimmunotherapy
   b) Primary refractory disease (partial response, no response, or progression) or relapsed disease <12 months after completion of initial treatment with chemoimmunotherapy in non-candidates for CAR T-cell therapy
   c) Alternative systemic therapy for relapsed/refractory disease in non-candidates for CAR T-cell therapy.[7]

Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

3. Treatment of adult patients; OR

For **NCCN** required criteria coverage:

4. Single agent or in combination with rituximab for one of the following:
   a) As primary therapy
   b) Continuation of primary therapy until symptomatic disease progression (beyond biochemical progression) or unacceptable toxicity

c) For relapse if previously used as primary therapy that was well tolerated and elicited a prolonged response
d) Alternative therapy for previously treated disease with persistent symptoms following primary therapy or that does not respond to primary therapy or for progressive or relapsed disease; OR

5. For the management of symptomatic Bing-Neel syndrome for one of the following:
   a) Single agent
   b) In combination with rituximab if systemic control is needed.[8]

Authorization Period and Renewal Criteria

1. Initial Authorization Period: 12 months
2. Renewal Criteria: No evidence of disease progression or unacceptable toxicity
3. Renewal Authorization Period: 12 months

Ibrutinib: References

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3. National Comprehensive Cancer Network. Hematopoietic Cell Transplantation (HCT). https://www.nccn.org/professionals/physician_gls/pdf/hct.pdf. Accessed December 3, 2024.
4. National Comprehensive Cancer Network. Hairy Cell Leukemia. https://www.nccn.org/professionals/physician_gls/pdf/hairy_cell.pdf. Accessed December 3, 2024.
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6. National Comprehensive Cancer Network. Central Nervous System Cancers. https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed December 3, 2024.
7. National Comprehensive Cancer Network. B-Cell Lymphomas. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed December 3, 2024.
8. National Comprehensive Cancer Network. Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma. https://www.nccn.org/professionals/physician_gls/pdf/waldenstroms.pdf. Accessed December 3, 2024.
9. McDonald et al. The role of Bruton's tyrosine kinase in the immune system and disease. https://pubmed.ncbi.nlm.nih.gov/34534359/. Accessed December 3, 2024.

Ibrutinib: Coding (CPT®, ICD 10, and HCPCS) *

*Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all-inclusive and is subject to updates. In addition, the codes listed are not a guarantee of payment. CPT codes are available through the AMA.

Code	Description
C79.31	Limited Brain Metastases, Extensive Brain Metastases
C83.0	Splenic Marginal Zone Lymphoma
C83.1	Mantle Cell Lymphoma
C83.3	Diffuse Large B-Cell Lymphoma, HIV-Related B-Cell Lymphomas
C83.39	Primary CNS Lymphoma
C83.8	High-Grade B-Cell Lymphomas
C88.0	Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma
C88.4	Extranodal Marginal Zone Lymphoma of the Stomach, Nodal Marginal Zone
C91.1	Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
C91.4	Hairy Cell Leukemia
D47.Z2	Post-Transplant Lymphoproliferative Disorders
J8999	Ibrutinib
Z94.84	Hematopoietic Cell Transplantation

Ibrutinib: Revision and Review History

No.	Description	Date(s)
1	Original Effective Date:	12/1/2024
2	Policy Review Dates:	
3	Policy Revision Dates:	
4	Department Owner:	Medical Affairs
5	NH Advisory Committee:	12/21/2024
6	Revision Changes:	