Clinical Policy: Ibrutinib (Imbruvica)

Reference Number: CP.PHAR.126
Effective Date: 10.01.15
Last Review Date: 02.24
Line of Business: Commercial, HIM, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Ibrutinib (Imbruvica®) is a Bruton tyrosine kinase (BTK) inhibitor.

FDA Approved Indication(s)

Imbruvica is indicated for the treatment of:

- Adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)
- Adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with 17p deletion
- Adult patients with Waldenström's macroglobulinemia (WM)
- Adult and pediatric patients age 1 year and older with chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Imbruvica is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (must meet all)**:**

1. Diagnosis of CLL or SLL;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. For Imbruvica requests, member must use generic ibrutinib, if available, unless contraindicated or clinically significant adverse effects are experienced;
5. Prescribed as a single agent;
6. Request meets one of the following (a, b, c, or d):*
   a. For capsules, dose ≤ 420 mg per day, and prescribed quantity does not exceed 3 capsules per day;
   b. For tablets, dose is 420 mg per day, and prescribed quantity does not exceed 1 tablet per day;
   c. For oral suspension, dose does not exceed 420 mg (6 mL) per day;
   d. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/HIM – 6 months
Commercial – 12 months or duration of request, whichever is less

B. Waldenström's Macroglobulinemia (must meet all)**:**
1. Diagnosis of WM or lymphoplasmacytic lymphoma, including symptomatic Bing-Neel syndrome;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. For Imbruvica requests, member must use generic ibrutinib, if available, unless contraindicated or clinically significant adverse effects are experienced;
5. Prescribed as a single agent or in combination with rituximab*;
   **Prior authorization may be required*
6. Request meets one of the following (a, b, c, or d):*
   a. For capsules, dose ≤ 420 mg per day, and prescribed quantity does not exceed 3 capsules per day;
   b. For tablets, dose is 420 mg per day, and prescribed quantity does not exceed 1 tablet per day;
   c. For oral suspension, dose does not exceed 420 mg (6 mL) per day;
   d. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).
   **Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/HIM – 6 months
Commercial – 12 months or duration of request, whichever is less

C. Chronic Graft-Versus-Host Disease (must meet all)**:**
1. Diagnosis of cGVHD;
2. Prescribed by or in consultation with an oncologist, hematologist, or bone marrow transplant specialist;
3. Age ≥ 1 year;
4. For Imbruvica requests, member must use generic ibrutinib, if available, unless contraindicated or clinically significant adverse effects are experienced;
5. Member has a history of bone marrow/stem cell transplant;
6. Member meets both of the following (a and b):
   a. Failure of a systemic corticosteroid (*see Appendix B*) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
   b. Failure of a systemic immunosuppressant (*see Appendix B*) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization may be required*
7. Imbruvica is not prescribed concurrently with Jakafi® or Rezurock®;
8. Request meets one of the following (a, b, c, or d):*
   a. For capsules, dose ≤ 420 mg per day, and prescribed quantity does not exceed 3 capsules per day;

b. For tablets, dose is 420 mg per day, and prescribed quantity does not exceed 1 tablet per day;
c. For oral suspension, dose does not exceed any of the following (i or ii):
   i. 420 mg (6 mL) per day;
   ii. For age 1 to < 12 years: 240 mg/m^2 per day;
d. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/HIM – 6 months
Commercial – 12 months or duration of request, whichever is less

D. NCCN Compendium Indications (off-label) (must meet all)**:**
1. Diagnosis of one of the following (a, b, c, or d):
   a. Primary CNS lymphoma;
   b. Brain metastases in lymphoma;
   c. Hairy cell leukemia (HCL);
   d. B-cell lymphoma subtype (i, ii, iii, iv, v, vi, or vii):
      i. HIV-related non-germinal center diffuse large B-cell lymphoma (DLBCL);
      ii. High-grade B-cell lymphoma;
      iii. Post-transplant lymphoproliferative disorder (PTLD);
      iv. DLBCL;
      v. Histologic transformation of CLL/SLL to DLBCL in patients with del(17p)/TP53 mutation;
      vi. Mantle cell lymphoma (MCL);
      vii. Marginal zone lymphoma (MZL) subtype (1, 2, 3, or 4):
         1) Gastric MALT lymphoma;
         2) Nongastric MALT lymphoma (noncutaneous);
         3) Nodal MZL;
         4) Splenic MZL;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. For Imbruvica requests, member must use generic ibrutinib, if available, unless contraindicated or clinically significant adverse effects are experienced;
5. For oral suspension requests at a dose > 420 mg per day, documentation supports inability to swallow oral capsules/tablets;
6. Member meets one of the following (a, b, c, or d):
   a. For primary CNS lymphoma, request is for use as either induction therapy or for relapsed or refractory disease;
   b. For brain metastases in lymphoma, request is for initial treatment in select cases (e.g., small asymptomatic brain metastases), or for treatment of recurrent or relapsed brain metastases;
   c. For B-cell lymphoma, one of the following (i, ii, or iii):
      i. For MCL only: Request is for use as either induction therapy or maintenance therapy;
      ii. For MCL only: Prescribed in combination with rituximab as pretreatment in order to limit the number of cycles of aggressive induction therapy with

RHyperCVAD (ritixumab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone);
iii. Received ≥ 1 prior line of systemic therapy (*see Appendix B*), unless contraindicated or clinically significant adverse effects are experienced to all;
d. For HCL, member has disease progression after therapy for relapsed/refractory disease *(see Appendix B)*;

7. Request meets one of the following (a, b, c, or d):*
   a. For capsules, dose ≤ 420 mg per day, and prescribed quantity does not exceed 3 capsules per day;
   b. For tablets, dose ≥ 420 mg per day, and prescribed quantity does not exceed 1 tablet per day;
   c. For oral suspension, dose does not exceed 420 mg (6 mL) per day;
   d. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

   **Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/HIM – 6 months
Commercial – 12 months or duration of request, whichever is less

E. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**

1. Documentation supports that member is currently receiving Imbruvica for a covered oncology-related indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. For Imbruvica requests, member must use generic ibrutinib, if available, unless contraindicated or clinically significant adverse effects are experienced;
4. For oral suspension requests at a dose > 420 mg per day, documentation supports continued inability to swallow oral capsules/tablets;
5. For cGVHD, Imbruvica is not prescribed concurrently with Jakafi or Rezurock;

6. If request is for a dose increase, request meets one of the following (a, b, or c):*
   a. CLL/SLL and WM: one of the following (i, ii, or iii):
      i. For capsules, new dose ≤ 420 mg per day, and prescribed quantity does not exceed 3 capsules per day;
      ii. For tablets, new dose is 420 mg per day, and prescribed quantity does not exceed 1 tablet per day;
      iii. For oral suspension, new dose does not exceed 420 mg (6 mL) per day;
   b. cGVHD: New dose does not exceed any of the following (i, ii, or iii):
      i. For capsules, new dose ≤ 420 mg per day, and prescribed quantity does not exceed 3 capsules per day;
      ii. For tablets, new dose is 420 mg per day, and prescribed quantity does not exceed 1 tablet per day;
      iii. For oral suspension, new dose does not exceed any of the following (1 or 2):
         1) 420 mg (6 mL) per day;
         2) For age 1 to < 12 years, 240 mg/m^2 per day;
   c. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

   **For oncology indications, prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/HIM – 12 months
Commercial – 12 months or duration of request, whichever is less

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

BTK: Bruton's tyrosine kinase
cGVHD: chronic graft-versus-host disease
CLL: chronic lymphocytic leukemia
DLBCL: diffuse large B-cell lymphoma
FDA: Food and Drug Administration
HCL: hairy cell leukemia
MALT: mucosa-associated lymphoid tissue
MCL: mantle cell lymphoma
MZL: marginal zone lymphoma
NCCN: National Comprehensive Cancer Network
PTLD: post-transplant lymphoproliferative disorders
SLL: small lymphocytic lymphoma
WM: Waldenström's macroglobulinemia

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Examples of systemic therapies for B-cell lymphomas		
Bendeka®, Treanda® (bendamustine) ± Rituxan (rituximab) or Gazyva® (obinutuzumab)	Varies	Varies
CHOP + Gazyva (obinutuzumab)		
EPOCH [etoposide, prednisone, vincristine (Vincasar PFS®), cyclophosphamide, doxorubicin (Adriamycin®)] + Rituxan (rituximab)		
NORDIC [dose-intensified induction immunochemotherapy with Rituxan (rituximab) + cyclophosphamide, vincristine (Vincasar PFS), doxorubicin, predisone] alternating with Rituxan (rituximab) and high-dose cytarabine		
RCEOP [Rituxan (rituximab), cyclophosphamide, etoposide, vincristine (Vincasar PFS), prednisone]		
RCEPP [Rituxan (rituximab), cyclosphosphamide, etoposide, prednisone, procarbazine]		
RCHOP [cyclophosphamide, doxorubicin (Adriamycin®), vincristine (Vincasar PFS), prednisone]/RDHAP		
RCVP [Rituxan (rituximab), cyclophosphamide, doxorubicin (Adriamycin®), vincristine (Vincasar PFS)]		
RDHAP [Rituxan (rituximab), dexamethasone, cytarabine, cisplatin]		
RDHAX [Rituxan (rituximab), dexamethasone, cytarabine, oxaliplatin]		
Revlimid® (lenalidomide) + Rituxan (rituximab)		
Rituxan (rituximab)		

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
VR-CAP [bortezomib (Velcade®), Rituxan (rituximab), cyclosphosphamide, doxorubicin (Adriamycin®), and prednisone]		
Examples of systemic corticosteroids and immunosuppressants for cGVHD		
Systemic corticosteroids (e.g., methylprednisolone, prednisone)	Varies	Varies
mycophenolate mofetil (Cellcept®)		
cyclosporine (Gengraf®, Neoral®, Sandimmune®)		
tacrolimus (Prograf®)		
sirolimus (Rapamune®)		
imatinib (Gleevec®)		
Jakafi® (ruxolitinib)		
Rezurock™ (belumosudil)		
Examples of systemic therapies for primary CNS lymphoma		
High-dose methotrexate-based regimen [methotrexate (Rheumatrex®) + Rituxan (rituximab) and other agents (e.g., temozolomide, vincristine (Vincasar PFS), procarbazine, cytarabine)]	Varies	Varies
Examples of systemic therapies for relapsed/refractory HCL		
Tafinlar® (dabrafenib) + Mekinist® (trametinib) (if not previously treated with BRAF inhibitor)	Varies	Varies
Zelboraf® (vemurafenib) ± rituximab (if not previously given)		
rituximab ± purine analog (e.g., cladribine, pentostatin)		
Pegasys® (peginterferon alfa-2a)		

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings
None reported

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
CLL/SLL, WM	420 mg PO QD	420 mg/day (3 capsules, 1 tablet, or 6 mL per day)
cGVHD	• Age ≥ 12 years and older: 420 mg PO QD • Age 1 to < 12 years: 240 mg/m^2 PO QD, up to a dose of 420 mg	420 mg/day (3 capsules, 1 tablet, or 6 mL per day)

VI. Product Availability

- Capsules: 70 mg, 140 mg
- Tablets: 140 mg, 280 mg, 420 mg
- Oral suspension: 70 mg/mL

VII. References

1. Imbruvica Prescribing Information. Sunnyvale, CA: Pharmacyclics LLC; May 2023. Available at: https://www.imbruvica.com/. Accessed October 12, 2023.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed November 28, 2023.
3. National Comprehensive Cancer Network. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Version 1.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed November 28, 2023.
4. National Comprehensive Cancer Network. B-cell Lymphomas Version 6.2023. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed November 28, 2023.
5. National Comprehensive Cancer Network. Hairy Cell Leukemia Version 1.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/hairy_cell.pdf. Accessed November 28, 2023.
6. National Comprehensive Cancer Network. Central Nervous System Cancers Version 1.2023. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed November 28, 2023.
7. National Comprehensive Cancer Network. Hematopoietic Cell Transplantation (HCT) Version 3.2023. Available at: https://www.nccn.org/professionals/physician_gls/pdf/hct.pdf. Accessed November 28, 2023.
8. National Comprehensive Cancer Network. Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma Version 1.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/waldenstroms.pdf. Accessed November 28, 2023.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q 2021 annual review: oral oncology generic redirection language added; for MCL, NCCN directed language inserted to clarify combination therapy with rituximab; for CLL/SCC, histologic transformation combination therapy added per NCCN; for MZL, subtypes delineated for clarity, therapy trials broadened beyond rituximab per NCCN; for cGVHD, trial requirement edited to require a systemic corticosteroid and an immunosuppressant agent per NCCN and the Imbruvica pivotal trial; Appendix B reorganized by B-cell lymphomas vs. other indications; references to HIM.PHAR.21 to revised to HIM.PA.154; references reviewed and updated.	11.09.20	02.21
Added language for Imbruvica, Rezurock and Jafaki not to be used concurrently since all are used for cGVHD. Updated Appendix B alternatives for cGVHD.	08.24.21	11.21
1Q 2022 annual review: removed indication for CLL/SLL histologic (Richter's) transformation per NCCN as it is now category 2B; added indication of lymphoplasmacytic lymphoma to WM criteria per NCCN; updated primary CNS lymphoma criterion that ibrutinib may	11.13.21	02.22

Reviews, Revisions, and Approvals	Date	P&T Approval Date
be used as either induction therapy or for relapsed or refractory disease per NCCN; clarified oral oncology generic redirection language to "must use"; references reviewed and updated.		
Revised approval duration for Commercial line of business from length of benefit to 12 months or duration of request, whichever is less	01.20.22	05.22
RT4: added pediatric expansion for cGVHD and new oral suspension formulation. Template changes applied to other diagnoses/ indications.	08.31.22	
Per Data Analytics, revised criteria to require inability to swallow oral capsules/tablets only when the requested oral suspension dose is > 420 mg per day. Template changes applied to continued therapy section.	10.04.22	
1Q 2023 annual review: changes made to align with current NCCN recommendations – removed combination use with Rituxan, Gazyva, or bendamustine for CLL/SLL (category 2B), added Bing-Neel syndrome as a WM subtype treatable with Imbruvica, removed follicular lymphoma as a NCCN compendial off-label indication (NCCN no longer supports use of Imbruvica for this indication), corrected the indication for "Histological transformation from MZL to DLBCL" to "Histological transformation from CLL/SLL to DLBCL"; for GvHD clarified that the requirement is for a prior trial of *both* a systemic corticosteroid and a systemic immunosuppressant to align with the previously P&T-approved approach for Rezurock for GvHD; references reviewed and updated.	11.17.22	02.23
RT4: removed previously approved FDA indications for MCL and MZL and converted to NCCN supported off-label indications; removed 560 mg tablet strength.	05.30.23	
1Q 2024 annual review: no significant changes; per NCCN recommendations, clarified that coverage is for symptomatic Bing-Neel syndrome only, added coverage criteria for off-label use for brain metastases in lymphoma, for histologic transformation of CLL/SLL to DLBCL clarified that coverage is for patients with del(17p)/TP53 mutation, and clarified that for HCL, use of Imbruvica is for members with disease progression after therapy for relapsed/refractory disease; references reviewed and updated.	11.28.23	02.24

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical

policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in 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.