Clinical Policy: Ibrutinib (Imbruvica)

Reference Number: CP.PHAR.126
Effective Date: 10.01.15
Last Review Date: 02.20
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 mantle cell lymphoma (MCL) who have received at least one prior therapy
  - Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
- 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 patients with marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy
  - Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
- Adult patients 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. Mantle Cell Lymphoma (must meet all)**:**

1. Diagnosis of MCL;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Member meets one of the following (a or b):
   a. Prescribed in combination with rituximab as pretreatment for HyperCVAD;

b. Received at least one prior therapy (*see Appendix B*), unless contraindicated or clinically significant adverse effects are experienced to all;

5. Request meets one of the following (a, b, or c):*
   a. For dose ≤ 420 mg per day, request is for capsules and prescribed quantity does not exceed 3 capsules per day;
   b. For dose ≥ 420 mg (not to exceed 560 mg) per day, request is for tablets and prescribed quantity does not exceed 1 tablet per day;
   c. 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 – Length of Benefit

B. 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. Prescribed as a single agent or in combination with one of the following (a, b, or c):
   a. Rituximab;
   b. Obinutuzumab;
   c. Bendamustine and rituximab;
5. Request meets one of the following (a, b, or c):*
   a. For dose ≤ 420 mg per day, request is for capsules and prescribed quantity does not exceed 3 capsules per day;
   b. For 420 mg dose per day, request is for tablets and prescribed quantity does not exceed 1 tablet per day;
   c. 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 – Length of Benefit

C. Waldenström's Macroglobulinemia (must meet all)**:**

1. Diagnosis of WM;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Prescribed as a single agent or in combination with rituximab;
5. Request meets one of the following (a, b, or c):*
   a. For dose ≤ 420 mg per day, request is for capsules and prescribed quantity does not exceed 3 capsules per day;
   b. For 420 mg dose per day, request is for tablets and prescribed quantity does not exceed 1 tablet per day;
   c. 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 – Length of Benefit

D. Marginal Zone Lymphoma (must meet all)**:**
1. Diagnosis of MZL;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Received at least one prior anti-CD20-based therapy (e.g., Rituxan®), unless contraindicated or clinically significant adverse effects are experienced to all;
5. Request meets one of the following (a, b, or c):*
   a. For dose ≤ 420 mg per day, request is for capsules and prescribed quantity does not exceed 3 capsules per day;
   b. For dose ≥ 420 mg (not to exceed 560 mg) per day, request is for tablets and prescribed quantity does not exceed 1 tablet per day;
   c. 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 – Length of Benefit

E. 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 ≥ 18 years;
4. Member has a history of bone marrow/stem cell transplant;
5. Member meets one of the following (a or b):
   a. Failure of a systemic corticosteroid (e.g., prednisone) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
   b. If intolerance or contraindication to systemic corticosteroids, failure of an immunosuppressant [e.g., mycophenolate mofetil, calcineurin inhibitors (e.g., cyclosporine, tacrolimus), sirolimus] at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
6. Request meets one of the following (a, b, or c):*
   a. For dose ≤ 420 mg per day, request is for capsules and prescribed quantity does not exceed 3 capsules per day;
   b. For 420 mg dose per day, request is for tablets and prescribed quantity does not exceed 1 tablet per day;
   c. 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 – Length of Benefit

F. NCCN Compendium Indications (off-label) (must meet all)**:**
1. Diagnosis of one of the following (a, b, or c):
   a. Non-Hodgkin's (B-cell) lymphoma or any of its subtypes (*see Appendix D for NCCN-recommended subtypes*);
   b. Hairy cell leukemia (HCL);
   c. Primary CNS lymphoma;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Disease is relapsed, recurrent, or progressive;
5. Member meets one of the following (a or b):
   a. For HCL: Received at least two prior therapies (*see Appendix B*), unless contraindicated or clinically significant adverse effects are experienced to all;
   b. For CNS lymphoma or non-Hodgkin's (B-cell) lymphoma: Received at least one prior therapy (*see Appendix B*), unless contraindicated or clinically significant adverse effects are experienced to all;
6. Request meets one of the following (a, b, or c):*
   a. For dose ≤ 420 mg per day, request is for capsules and prescribed quantity does not exceed 3 capsules per day;
   b. For dose ≥ 420 mg (not to exceed 560 mg) per day, request is for tablets and prescribed quantity does not exceed 1 tablet per day;
   c. 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 – Length of Benefit

G. Other diagnoses/indications
1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**
1. Currently receiving medication via Centene benefit, or 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. If request is for a dose increase, request meets one of the following (a, b, or c):*
   a. MCL and MZL: New dose does not exceed 560 mg per day and one of the following (i or ii):
      i. For dose ≤ 420 mg per day, request is for capsules and prescribed quantity does not exceed 3 capsules per day;
      ii. For dose ≥ 420 mg (not to exceed 560 mg) per day, request is for tablets and prescribed quantity does not exceed 1 tablet per day;

b. CLL/SLL, WM, and cGVHD: New dose does not exceed 420 mg and one of the following (i or ii):
   i. For dose ≤ 420 mg per day, request is for capsules and prescribed quantity does not exceed 3 capsules per day;
   ii. For 420 mg dose per day, request is for tablets and prescribed quantity does not exceed 1 tablet 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 – Length of Benefit

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 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.PHAR.21 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
FL: follicular lymphoma
HCL: hairy cell leukemia
HyperCVAD: cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine
MALT: mucosa-associated lymphoid tissue
MCL: mantle cell lymphoma
MZL: marginal zone lymphoma
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
Prior Line Regimens for Oncology Indications		
EPOCH [etoposide, prednisone, vincristine (Vincasar PFS®), cyclophosphamide, doxorubicin (Adriamycin®)] + Rituxan® (rituximab)	**DLBCL** Varies	Varies
RCHOP [cyclophosphamide, doxorubicin (Adriamycin®), vincristine (Vincasar PFS®), prednisone]/RDHAP	**DLBCL, FL, MCL, MZL, PTLD** Varies	Varies
HyperCVAD [cyclophosphamide, vincristine (Vincasar PFS®), doxorubicin (Adriamycin®), dexamethasone] + Rituxan® (rituximab)	**MCL** Varies	Varies
NORDIC [dose-intensified induction immunochemotherapy with Rituxan® (rituximab) + cyclophosphamide, vincristine (Vincasar PFS®), doxorubicin, predisone] alternating with Rituxan® (rituximab) and high-dose cytarabine	**MCL** Varies	Varies
RDHAP [Rituxan® (rituximab), dexamethasone, cytarabine, cisplatin]	**MCL** Varies	Varies
RDHAX [Rituxan® (rituximab), dexamethasone, cytarabine, oxaliplatin]	**MCL** Varies	Varies
VR-CAP [bortezomib (Velcade®), Rituxan® (rituximab), cyclosphosphamide, doxorubicin (Adriamycin®), and prednisone]	**MCL** Varies	Varies
Bendeka®, Treanda® (bendamustine) + Rituxan® (rituximab)	**MCL, FL** Varies	Varies
Revlimid® (lenalidomide) + Rituxan® (rituximab)	**FL** Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Rituxan® (rituximab)	**FL, HCL, MZL, PTLD** Varies	Varies
RCVP [Rituxan® (rituximab), cyclophosphamide, doxorubicin (Adriamycin®), vincristine (Vincasar PFS®)]	**FL, MZL, PTLD** Varies	Varies
Bendeka®, Treanda® (bendamustine) + Gazyva® (obinutuzumab)	**FL** Varies	Varies
CHOP + Gazyva® (obinutuzumab)	**FL** Varies	Varies
cladribine	**HCL** 0.09 mg/kg/day IV for 7 days (1 cycle)	0.09 mg/kg/day per cycle (7 days)
Intron® A (interferon alfa-2b)	**HCL** 2 million units/m^2 TIW	6 million units/m^2/week
Nipent™ (pentostatin)	**HCL** 4 mg/m^2 IV every other week	4 mg/m^2 IV every 2 weeks
High-dose methotrexate-based regimen [methotrexate (Rheumatrex®) + Rituxan® (rituximab) and other agents (e.g., temozolomide, vincristine (Vincasar PFS®), procarbazine, cytarabine)]	**Primary CNS Lymphoma** Varies	Varies
RCEPP [Rituxan® (rituximab), cyclosphosphamide, etoposide, prednisone, procarbazine]	**PTLD** Varies	Varies
RCEOP (Rituxan® [rituximab), cyclophosphamide, etoposide, vincristine (Vincasar PFS®), prednisone]	**PTLD** Varies	Varies
Immunosuppressive Agents		
mycophenolate mofetil (Cellcept®)	**cGVHD*** 2 g/day PO	2 g/day
cyclosporine (Gengraf®, Neoral®, Sandimmune®)	**cGVHD*** 2 g/day PO	Varies
tacrolimus (Prograf®)	**cGVHD***	1 g/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	1g/day PO or 0.06 mg/kg PO BID	
sirolimus (Rapamune®)	**cGVHD*** 6 mg loading dose PO, then 2 mg PO QD	Maintenance: 2 mg/day
systemic corticosteroids (e.g., prednisone, prednisolone, methylprednisolone)	**cGVHD*** An equivalent dose of prednisone 1 mg/kg/day PO	Varies

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.
**Off-label*

Appendix C: Contraindications/Boxed Warnings
None reported

Appendix D: General Information
- cGVHD:
  - The National Institutes of Health Working Group recommends that the diagnosis of cGVHD require at least 1 diagnostic manifestation of cGVHD (e.g., poikiloderma or esophageal web) or at least 1 distinctive manifestation (e.g., keratoconjunctivitis sicca) confirmed by pertinent biopsy or other relevant tests in the same or another organ.
  - Corticosteroids are the mainstay of initial systemic treatment for patients with cGVHD. Alternatives to, or add-on therapy to corticosteroids includes but is not limited to: mycophenolate mofetil, calcineurin inhibitors (e.g., cyclosporine, tacrolimus), sirolimus.
  - Steroid-refractory chronic GVHD is defined as either failure to improve after at least 2 months, or progression after 1 month of standard immunosuppressive therapy, including corticosteroids and cyclosporine.
- Non-Hodgkin's (B-cell) lymphoma subtypes supported as NCCN category 2A recommended uses for Imbruvica:
  - Follicular lymphoma (grade 1-2)
  - Gastric MALT lymphoma
  - Nongastric MALT lymphoma
  - Nodal marginal zone lymphoma
  - Splenic marginal zone lymphoma
  - Histologic Transformation of Marginal Zone Lymphoma to Diffuse Large B-Cell Lymphoma
  - Diffuse large B-cell lymphoma
  - AIDS-related non-germinal center diffuse large B-cell lymphoma
  - Post-transplant lymphoproliferative disorders
- MCL:

- Imbruvica in combination with Rituxan as a pre-treatment to limit the number of cycles of HyperCVAD with Rituxan is recommended category 2A per NCCN guidelines.

- MZL:
  - Imbruvica as a second-line or later agent is recommended category 2A per NCCN guidelines for MZL subtypes including gastric mucosa-associated lymphoid tissue (MALT) lymphoma, nongastric MALT lymphoma, splenic marginal zone lymphoma, and nodal marginal zone lymphoma.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
MCL and MZL	560 mg PO QD	560 mg/day (3 capsules or 1 tablet per day)
CLL/SLL, WM, and cGVHD	420 mg PO QD	420 mg/day (3 capsules or 1 tablet per day)

VI. Product Availability

- Capsules: 70 mg, 140 mg
- Tablets: 140 mg, 280 mg, 420 mg, 560 mg

VII. References

1. Imbruvica Prescribing Information. Sunnyvale, CA: Pharmacyclics LLC; April 2020. Available at: https://www.imbruvica.com/. Accessed April 28, 2020.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed November 22, 2019.
3. National Comprehensive Cancer Network Guidelines. B-cell lymphomas Version 6.2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed November 22, 2019.
4. Ruutu T, Gratwohl A, de Witte T, et al. Prophylaxis and treatment of GVHD: EBMT-ELN working group recommendations for a standardized practice. Bone Marrow Transplant. 2014 Feb;49(2):168-73.
5. Lee SJ, Vogelsang G, Flowers ME. Chronic graft-versus-host disease. Biol Blood Marrow Transplant 2003; 9:215-233.
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7. National Comprehensive Cancer Network. Hairy Cell Leukemia Version 1.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/hairy_cell.pdf. Accessed November 22, 2019.
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10. National Comprehensive Cancer Network. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Version 2.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed November 22, 2019.
11. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed November 22, 2019.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Changed 'and' to 'or' in I.E.1 per package insert Updated disclaimer language	01.16	
Policy converted to new template. Removed age and prescriber specialty requirements. Removed question related to moderate or severe hepatic impairment as it is not listed as a contraindication per PI. Added maximum dosage requirement for MCL, CLL/SLL, and WM. Modified CLL/SLL criteria to allow use of Imbruvica as first line therapy for members without 17p deletion per PI and NCCN compendium. Added disease progression or unacceptable toxicity to reasons to discontinue per PI.	07.16	10.16
Added new FDA approved indication: MZL. MCL: added off-label use per NCCN compendium. CLL/SLL: removed "with or without 17p deletion" as that has no impact on coverage. Other diagnoses/indications: added hairy cell leukemia per NCCN compendium. Continued approval: Removed reasons to discontinue. Added requirement for documentation of positive response to therapy.	03.17	03.17
Converted to new template. Added new FDA approved indication: cGVHD. Increased continued approval duration from 6 to 12 months. Created criteria for hairy cell leukemia per NCCN guidelines/compendium. Added Appendix B: General Information.	08.09.17	11.17
3Q 2018 annual review: Policies combined for commercial, HIM, and Medicaid lines of business; For all lines of business: off-label NCCN compendium-supported uses were added, tablet formulations were added, age requirement was added for FDA-labeled indications, specialist requirement was added for all indications; For commercial: added off-label use of ibrutinib pretreatment for MCL per NCCN guidelines; For Medicaid, removed age requirement for pretreatment use of ibrutinib for MCL per NCCN guidelines; references reviewed and updated.	05.15.18	08.18
Per SDC, added preferencing for capsule formulation.	10.05.18	

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q 2019 annual review: for CLL/SLL, added requirement for single agent use per updated NCCN guidelines since combo use is category 2B; for FL, revised requirement of trial and failure to one prior therapy instead of two per updated NCCN guidelines; for CNS lymphoma, added hematologist prescriber option; consolidated criteria for NCCN compendium off-label uses; references reviewed and updated.	11.06.18	02.19
1Q 2020 annual review: no significant changes; references reviewed and updated.	11.26.19	02.20
RT4: modified CLL/SLL and WM criteria to allow combination use per updated FDA labeling (indication language remains unchanged). Revised maximum quantity by dose to maximize dose form cost effectiveness per data analytics recommendation; removed requirement for medical justification why capsules cannot be used.	04.28.20	

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.

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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.