Clinical Policy: Ibrutinib (Imbruvica)

Reference Number: CP.PHAR.126
Effective Date: 10.01.15
Last Review Date: 08.18 Revision Log
Line of Business: Commercial, HIM, Medicaid

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

Description

Ibrutinib (Imbruvica®) is an inhibitor of Bruton's tyrosine kinase (BTK).

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. If request is for tablets, medical justification supports inability to use capsules;
6. Dose does not exceed 560 mg per day (4 capsules or 1 tablet per day).

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. If request is for tablets, medical justification supports inability to use capsules;
5. Dose does not exceed 420 mg per day (3 capsules or 1 tablet per day).

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. If request is for tablets, medical justification supports inability to use capsules;
5. Dose does not exceed 420 mg per day (3 capsules or 1 tablet per day).

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. If request is for tablets, medical justification supports inability to use capsules;
6. Dose does not exceed 560 mg per day (4 capsules or 1 tablet per day).

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. If request is for tablets, medical justification supports inability to use capsules;
7. Dose does not exceed 420 mg per day (3 capsules or 1 tablet per day).

Approval duration:
Medicaid/HIM – 6 months
Commercial – Length of Benefit

F. Non-Hodgkin's Lymphoma and Subtypes (off-label) (must meet all)**:**
1. Diagnosis of non-Hodgkin's lymphoma or any of its subtypes (a, b, c, or d):
   a. Non-germinal center diffuse large B-cell lymphoma (DLBCL);
   b. Follicular lymphoma (FL);
   c. Hairy cell leukemia (HCL);
   d. Post-transplant lymphoproliferative disorder (PTLD);
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Disease is relapsed, recurrent, or progressive;
4. Member meets one of the following (a or b):
   a. For FL and HCL: Received at least two prior therapies (*see Appendix B*), unless contraindicated or clinically significant adverse effects are experienced to all;
   b. For DLBCL and PTLD: Received at least one prior therapy (*see Appendix B*), unless contraindicated or clinically significant adverse effects are experienced to all;
5. If request is for tablets, medical justification supports inability to use capsules;
6. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval duration:
Medicaid/HIM – 6 months
Commercial – Length of Benefit

G. Primary CNS Lymphoma (off-label) (must meet all):
1. Diagnosis of primary CNS lymphoma;
2. Prescribed by or in consultation with an oncologist;
3. Disease is relapsed or refractory;
4. Received at least one prior therapy (e.g., radiation therapy, high-dose methotrexate-based regimen, high-dose chemotherapy with stem cell rescue);
5. If request is for tablets, medical justification supports inability to use capsules;
6. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval duration:
Medicaid/HIM – 6 months

Commercial – Length of Benefit

H. 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 an 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: 560 mg per day (4 capsules or 1 tablet per day);
   b. CLL/SLL, WM, and cGVHD: 420 mg per day (3 capsules or 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*).

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
Chemotherapy Regimens		
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),	**MCL** Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
cyclosphosphamide, doxorubicin (Adriamycin®), and prednisone]		
Bendeka®, Treanda® (bendamustine) + Rituxan® (rituximab)	**MCL, FL** Varies	Varies
Revlimid® (lenalidomide) + Rituxan® (rituximab)	**FL** Varies	Varies
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

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
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*** 1g/day PO or 0.06 mg/kg PO BID	1 g/day
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
Not applicable

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.
- DLBCL:
  - The management of AIDS-related non-germinal center diffuse large B-cell lymphoma relapse and nongastric MALT lymphomas with concurrent large cell transformation should follow the treatment recommendations for DLBCL per NCCN guidelines.
- 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, non gastric 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
CLL/SLL, WM, and cGVHD	420 mg PO QD	420 mg/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; February 2018. Available at: https://www.imbruvica.com/. Accessed May 15, 2018.
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3. National Comprehensive Cancer Network Guidelines. B-cell lymphomas Version 4.2018. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed May 15, 2018.
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.
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7. National Comprehensive Cancer Network. Hairy Cell Leukemia Version 2.2018. Available at: https://www.nccn.org/professionals/physician_gls/pdf/hairy_cell.pdf. Accessed May 15, 2018.
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9. National Comprehensive Cancer Network. Central Nervous System Cancers Version 1.2018. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed May 15, 2018.

10. National Comprehensive Cancer Network. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Version 5.2018. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed May 15, 2018.
11. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed May 15, 2018.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy developed	09.15	09.15
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
No significant changes: per SDC chair, added preferencing for capsule formulation as more cost effective	10.23.18	

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.

For Health Insurance Marketplace members, when applicable, this policy applies only when the prescribed agent is on your health plan approved formulary. Request for non-formulary drugs must be reviewed using the formulary exception policy.