Clinical Policy Title:	ibrutinib
Policy Number:	RxA.170
Drug(s) Applied:	Imbruvica®
Original Policy Date:	02/07/2020
Last Review Date:	06/10/2021
Line of Business Policy Applies to:	All lines of business

Background

Ibrutinib is a bruton tyrosine kinase (BTK) inhibitor 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.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
ibrutinib (Imbruvica®)	MCL and MZL	560 mg by mouth once daily	560 mg/day
	CLL/SLL, WM, and cGVHD	420 mg by mouth once daily	420 mg/day

Dosage Forms

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

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

A. 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. Member is 18 years of age or older;
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 there is a 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 experience;
6. Request meets one of the following (a or b):
   a. Dose does not exceed 420 mg (3 capsules or 1 tablet) per day;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*Prescriber must submit supporting evidence*).

Approval Duration
Commercial: 6 months
Medicaid: 6 months

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. Member is 18 years of age or older;
4. Prescribed as a single agent or in combination with one of the following (a, b, or c):
   a. rituximab;
   b. obinutuzumab; or
   c. bendamustine and rituximab;
5. Request meets one of the following (a or b):
   a. Dose does not exceed 420 mg (3 capsules or 1 tablet) per day;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*Prescriber must submit supporting evidence*).

Approval Duration
Commercial: 6 months
Medicaid: 6 months

C. Mantle Cell Lymphoma (must meet all)**:**

1. Diagnosis of MCL;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Member is 18 years or older;
4. Member meets one of the following (a or b):
   a. Prescribed in combination with rituximab as pre-treatment for HyperCVAD;
   b. Received at least one (1) prior therapy (*see Appendix B*), unless contraindicated or clinically significant adverse effects are experienced to all;
5. Request meets one of the following (a or b):
   a. Dose does not exceed 560 mg (4 capsules or 1 tablet) per day;

b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*Prescriber must submit supporting evidence*).

Approval Duration
Commercial: 6 months
Medicaid: 6 months

D. Marginal Zone Lymphoma (must meet all)**:**

1. Diagnosis of MZL;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Member is 18 years of age or older;
4. Received at least one (1) prior anti-CD20-based therapy (e.g., rituximab), unless contraindicated or clinically significant adverse effects are experienced to all;
5. Request meets one of the following (a or b):
   a. Dose does not exceed 560 mg (4 capsules or 1 tablet) per day;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*Prescriber must submit supporting evidence*).

Approval Duration
Commercial: 6 months
Medicaid: 6 months

E. Waldenstrom's Macroglobulinemia (must meet all)**:**

1. Diagnosis of WM;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Member is 18 years of age or older;
4. Prescribed as a single agent or in combination with rituximab;
5. Request meets one of the following (a or b):
   a. Dose does not exceed 420 mg (3 capsules or 1 tablet) per day;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval Duration
Commercial: 6 months
Medicaid: 6 months

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. Member is 18 years of age or older;
4. Disease is relapsed, recurrent, or progressive;
5. Member meets one of the following (a or b):
   a. For HCL: Received at least two (2) 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 (1) prior therapy (*see Appendix B*), unless contraindicated or clinically significant adverse effects are experienced to all;

6. Dose does not exceed FDA prescribing guidelines or dosing is supported by evidence-based guidelines or peer-reviewed literature for the relevant off-label use.

Approval Duration
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

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

1. Member is currently receiving medication that has been authorized by RxAdvance, 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 (4 capsules or 1 tablet) per day;
   b. CLL/SLL, WM, and cGVHD: New dose does not exceed 420 mg (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
Commercial: 12 months
Medicaid: 12 months

III. Appendices

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

Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

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, prednisone] 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), cyclophosphamide, doxorubicin (Adriamycin®), and prednisone]	**MCL** Varies	Varies
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

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
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™ (pentaostatin)	**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), cyclophosphamide, etoposide, prednisone, procarbazine]	**PTLD** Varies	Varies
RCEOP (Rituxan® [rituximab), cyclophosphamide, etoposide, vincristine (Vincasar PFS®), prednisone]	PTLD Varies	Varies
mycophenolate mofetil (Cellcept®)	**cGVHD*** 2 g/day PO	2 g/day
Immunosuppressive Agents		
cyclosporine (Gengraf®, Neoral®, Sandimmune®)	**cGVHD*** 2 g/day PO	Varies
tacrolimus (Prograf®)	**cGVHD*** 1g/day PO or 0.06 mg/kg POBID	1 g/day
sirolimus (Rapamune®)	**cGVHD*** 6 mg loading dose PO, then 2 mg PO once daily	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

- Contraindication(s):
  - None reported.

- Boxed Warning(s):
  - 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 ibrutinib:
  - Follicular lymphoma (grade 1-2)
  - Gastric MALT lymphoma
  - Nongastric MALT lymphoma (noncutaneous)
  - 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
  - High-Grade B-Cell Lymphomas with Translocations of MYC and BCL2 and/or BCL6 (double/triple hit lymphoma)
  - High-Grade B-Cell Lymphomas NOS
  - 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.

References

1. Imbruvica® Prescribing Information. Sunnyvale, CA: Pharmacyclics LLC; December 2020. Available at: https://www.imbruvica.com/files/prescribing-information.pdf . Accessed April 13, 2021.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed April 13, 2021.
3. National Comprehensive Cancer Network Guidelines. B-cell lymphomas Version 3.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf . Accessed April 13, 2021.
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): 168-173. Accessed April 13, 2021.
5. Lee SJ, Vogelsang G, Flowers ME. Chronic graft-versus-host disease. Biology of Blood and Marrow Transplant 2003; 9:215-233. Accessed April 13, 2021.
6. Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. Diagnosis and Staging Working Group Report. Biol Blood Marrow Transplant. 2005 Dec;11(12):945-956. Accessed April 13, 2021.
7. National Comprehensive Cancer Network. Hairy Cell Leukemia Version 2.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/hairy_cell.pdf . Accessed April 13, 2021.
8. Clinical Pharmacology [database online] powered by ClinicalKey. Tampa, FL: Elsevier, 2020. Accessed with subscription at: http://www.clinicalkey.com . Accessed April 13, 2021.
9. National Comprehensive Cancer Network. Central Nervous System Cancers Version 4.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf . Accessed April 13, 2021.
10. National Comprehensive Cancer Network. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Version 3.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf . Accessed April 13, 2021.
11. Ibrutinib. Micromedex Solutions. Truven Health Analytics, Inc. Ann Arbor, MI; 2020, March 17. Accessed with subscription at: http://www.micromedexsolutions.com . Accessed April 13, 2021.
12. Ibrutinib, Lexi-Drug. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Accessed with subscription at: http://online.lexi.com . Accessed April 13, 2021.

Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established.	01/2020	02/07/2020
Policy was reviewed: 1. Policy title table was updated: Clinical Policy Title was updated to "ibrutinib"; Drug(s) Applied was updated to "Imbruvica®"; Line of Business Policy Applies to was updated to "All". 2. Clinical policy was updated: Approval duration was updated for both Initial and Continued Approval Criteria; Continued Approval was rephrased to "Currently receiving medication that has been authorized by RxAdvance…".; Removed preference to capsules over tablets; Updated CLL/SLL and WM criteria to allow combination use per package insert labelling update. 3. References were updated.	08/03/2020	09/14/2020
Policy was reviewed: 1. Clinical Policy title was updated. 2. Continued Therapy criteria II.A.1 was rephrased to "Member is currently receiving medication that has been authorized by RxAdvance..." 3. References were updated.	04/13/2021	06/10/2021