Clinical Policy: Ibrutinib (Imbruvica)

Reference Number: ERX.SPA.08
Effective Date: 04.01.17
Last Review Date: 11.21
Line of Business: Commercial, 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*
- Adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)
- Adult patients with CLL/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*
- Adult patients with chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic 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*

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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Imbruvica is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Mantle Cell Lymphoma (*B-cell lymphoma subtype*) (must meet all)**:**

1. Diagnosis of MCL (a B-cell lymphoma subtype);
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. For Imbruvica requests, medical justification supports inability to use ibrutinib, if available (e.g., contraindications to excipients);
5. Member meets one of the following (a or b):
   a. Prescribed in combination with rituximab as pretreatment in order to limit the number of cycles of aggressive induction therapy with RHyperCVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone);
   b. Received ≥ 1 prior line of systemic therapy (*see Appendix B*);
   **Prior authorization may be required*
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 – 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. For Imbruvica requests, medical justification supports inability to use ibrutinib, if available (e.g., contraindications to excipients);
5. Prescribed as a single agent or in combination with one of the following (a, b, c, or d):
   a. Rituxan® (rituximab);
   b. Gazyva® (obinutuzumab);
   c. Bendamustine and Rituxan;
   d. For histologic (Richter's) transformation of CLL/SLL to diffuse large B-cell lymphoma (DLBCL), Opdivo® (nivolumab) or Keytruda® (pembrolizumab), or refer to off-label DLBCL criteria;

   **Prior authorization may be required*
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 – 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. For Imbruvica requests, medical justification supports inability to use ibrutinib, if available (e.g., contraindications to excipients);
5. Prescribed as a single agent or in combination with Rituxan;

   **Prior authorization may be required*
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 – 6 months
Commercial – Length of Benefit

D. Marginal Zone Lymphoma (*B-cell lymphoma subtype*) (must meet all)**:**
1. Diagnosis of one of the following MZL subtypes (a, b, c, or d):
   a. Gastric MALT lymphoma;
   b. Nongastric MALT lymphoma (noncutaneous);
   c. Nodal MZL;
   d. Splenic MZL;

2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. For Imbruvica requests, medical justification supports inability to use ibrutinib, if available (e.g., contraindications to excipients);
5. Received ≥ 1 prior line of systemic therapy (*see Appendix B*);
   **Prior authorization may be required*
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 – 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. For Imbruvica requests, medical justification supports inability to use ibrutinib, if available (e.g., contraindications to excipients);
5. Member has a history of bone marrow/stem cell transplant;
6. Member meets one 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, 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*).

Approval duration:
Medicaid – 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. Primary CNS lymphoma;
   b. Hairy cell leukemia (HCL);
   c. B-cell lymphoma subtype (i, ii, iii, iv, v, or vi):
      i. AIDS-related non-germinal center DLBCL;
      ii. High-grade B-cell lymphoma;
      iii. Follicular lymphoma (grade 1-2) (FL);
      iv. Post-transplant lymphoproliferative disorder (PTLD);
      v. DLBCL;
      vi. Histologic transformation of MZL to DLBCL;

2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. For Imbruvica requests, medical justification supports inability to use ibrutinib, if available (e.g., contraindications to excipients);
5. Member meets one of the following (a or b):
   a. For primary CNS lymphoma or B-cell lymphoma, received ≥ 1 prior line of systemic therapy (*see Appendix B*);
   b. For HCL, received ≥ 2 prior lines of systemic therapies (*see Appendix B*);
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 – 6 months
Commercial – Length of Benefit

G. Other diagnoses/indications
1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions, 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. For Imbruvica requests, medical justification supports inability to use ibrutinib, if available (e.g., contraindications to excipients);
4. For cGVHD, Imbruvica is not prescribed concurrently with Jakafi or Rezurock;
5. 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 – 12 months
Commercial – Length of Benefit

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.

Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. 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 policy – ERX.PA.01 or evidence of coverage documents.

III. 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
MALT: mucosa-associated lymphoid tissue
MCL: mantle cell lymphoma
NCCN: National Comprehensive Cancer Network
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
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)		
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®)		

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
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 HCL		
Pegasys® (peginterferon alfa-2b)	Varies	Varies
cladribine		
Nipent™ (pentostatin)		

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

IV. Dosage and Administration

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

V. Product Availability

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

VI. References

1. Imbruvica Prescribing Information. Sunnyvale, CA: Pharmacyclics LLC; August 2020. Available at: https://www.imbruvica.com/. Accessed November 9, 2020.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed November 9, 2020.
3. National Comprehensive Cancer Network Guidelines. B-cell lymphomas Version 4.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed November 9, 2020.
4. National Comprehensive Cancer Network. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Version 1.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed November 22, 2019.
5. National Comprehensive Cancer Network. Hematopoietic Cell Transplantation (HCT): Pre-Transplant Recipient Evaluation and Management of Graft-Versus-Host Disease Version 2.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/hct.pdf. Accessed November 9, 2020.
6. National Comprehensive Cancer Network. Hairy Cell Leukemia Version 1.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/hairy_cell.pdf. Accessed November 9, 2020.
7. National Comprehensive Cancer Network. Central Nervous System Cancers Version 3.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed November 9, 2020.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	01.17	02.17
Added new FDA approved indication: cGVHD.	08.29.17	11.17

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Added criteria for hairy cell leukemia per NCCN guidelines/compendium. Re-auth: updated to include cGVHD; added requirement for positive response to therapy.		
3Q 2018 annual review: off-label NCCN compendium-supported uses added; tablet formulations added; age requirement added for FDA-labeled indications; specialist requirement added for all indications; off-label use of ibrutinib pretreatment for MCL added per NCCN guidelines; references reviewed and updated.	05.15.18	08.18
1Q 2019 annual review: added preferencing for capsule formulation; 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.	10.30.18	02.19
1Q 2020 annual review: no significant changes; added Medicaid line of business with 6/12 month approval durations; 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	
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 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

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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.