Clinical Policy: Ibrutinib (Imbruvica)

Reference Number: PA.CP.PHAR.126
Effective Date: 10/15
Last Review Date: 01/19

Coding Implications
Revision Log

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
It is the policy of health plans affiliated with Pennsylvania Health and Wellness that Imbruvica is **medically necessary** when one of 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. 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;
4. If request is for tablets, medical justification supports inability to use capsules;
5. Request meets one of the following (a or b):
   a. Dose does not exceed 560 mg per day (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: 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. If request is for tablets, medical justification supports inability to use capsules;
4. Request meets one of the following (a or b):
   a. Dose does not exceed 420 mg per day (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: 6 months

C. Waldenström's Macroglobulinemia (must meet all)**:**
1. Diagnosis of Waldenström's macroglobulinemia (WM);
2. Prescribed by or in consultation with an oncologist or hematologist;
3. If request is for tablets, medical justification supports inability to use capsules;
4. 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: 6 months

D. Marginal Zone Lymphoma (must meet all)**:**
1. Diagnosis of marginal zone lymphoma (MZL);
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Member has received at least one prior anti-CD20-based therapy (e.g., rituximab), unless contraindicated or clinically significant adverse effects are experienced to all;
4. If request is for tablets, medical justification supports inability to use capsules;
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: 6 months

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. 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: 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. 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. If request is for tablets, medical justification supports inability to use capsules;
7. Request meets one of the following (a or b):
   a. Dose does not exceed FDAA maximum;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval duration: 6 months

G. Other diagnoses/indications: Refer to PA.CP.PMN.53

II. Continued Approval

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

1. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met all initial approval criteria or Continuity of Care Policy (PA.LTSS.PHAR.01) applies;
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: 6 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via Pennsylvania Health and Wellness benefit and documentation supports positive response to therapy or Continuity of Care Policy (PA.LTSS.PHAR.01) applies; **Approval duration: Duration of request or 6 months (whichever is less);** or
2. Refer to PA.CP.PMN.53

Background

Description/Mechanism of Action:

Ibrutinib is a small-molecule inhibitor of Bruton's tyrosine kinase (BTK). Ibrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. BTK's role in signaling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis, and adhesion. Nonclinical studies show that ibrutinib inhibits malignant B-cell proliferation and survival in vivo as well as cell migration and substrate adhesion in vitro.

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
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		

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
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.

IV. 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

V. Product Availability

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

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
N/A	

Reviews, Revisions, and Approvals	Date	Approval Date
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.		
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.	01/19	

References

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