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Subject: Ibrutinib (Imbruvica®)

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DESCRIPTION:

Ibrutinib (Imbruvica) was initially approved by the U.S. Food and Drug Administration (FDA) in November 2013 for treatment of mantle cell lymphoma (MCL) in individuals who have received at least one prior therapy, and, in February 2014, for chronic lymphocytic leukemia (CLL) in individuals who have received at least one prior therapy (with or without a 17p deletion). Ibrutinib was later FDA approved for the treatment of CLL in individuals with a 17p deletion (July 2014), including those who are treatment naïve, and for the treatment of patients with Waldenström's Macroglobulinemia (January 2015). In March 2016, the indication was expanded to include first-line treatment of CLL in patients without a 17p deletion. Previously, first-line CLL treatment was limited to patients with a 17p deletion. In May 2016, the labeling was updated to include clinical trial results (Study 4) and dosing information for the use of ibrutinib in combination with bendamustine. In January 2017, ibrutinib was FDA approved for the treatment of patients with marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy. In August 2017, ibrutinib was FDA approved for the treatment of adult patients with chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy. In January 2019, the indication of CLL/SLL was expanded to include combination treatment with obinutuzumab (Gazyva) based on the positive results of the iLLUMINATE trial in treatment naïve patient and became the first non-chemotherapy combination regimen for this indication. In April 2020, the indication of CLL/SLL was expanded to include combination treatment with rituximab, based on the positive results of the E1912 study in untreated, 70 years or younger CLL/SLL patients. In August 2022, the cGVHD indication was expanded to include younger patients. The updated indication now reads “for the treatment of adult and pediatric patients age 1 year and older with cGVHD after failure of one or more lines of systemic therapy”. With the expanded age group, the manufacturer also introduced a 70 mg/mL oral suspension. In April 2023, AbbVie announced the intent to voluntarily withdraw the accelerated Imbruvica approvals for mantle cell lymphoma (MCL) and marginal zone

lymphoma (MZL) due to insufficient results from the confirmatory trials. This also led to the withdrawal of the 560 mg tablet strength as MCL and MZL were the only FDA-approved indication that had that daily dose. The NCCN guidelines continue to include category 2A recommendations regarding the use of ibrutinib in the treatment of MCL and MZL.

Prior to FDA approval ibrutinib received orphan drug status for the treatment of MCL (December 2012), CLL (February 2012), WM (October 2013), nodal MZL (February 2015), splenic MZL (February 2015), extranodal MZL (mucosa associated lymphoid tissue [MALT type] lymphoma) (February 2016), and cGVHD (June 2016). Ibrutinib, as sponsored by the innovator drug company, also has orphan designations for diffuse large B-cell lymphoma (October 2013), follicular lymphoma (September 2014), pancreatic cancer (June 2017), and gastric cancer, including gastroesophageal junction adenocarcinoma (February 2018).

Ibrutinib inhibits Bruton's tyrosine kinase to inhibit enzymatic activity and malignant B-cell proliferation and survival. Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is a mature B-cell lymphoma and comprises approximately 7% of newly diagnosed cases of Non-Hodgkin's Lymphoma (NHL). CLL and SLL are different manifestation of the same disease and are managed in much the same way. The main difference is that in CLL the abnormal lymphocytes are found in bone marrow and blood, while in SLL they are predominately found in the lymph nodes and bone marrow.

National Comprehensive Cancer Network (NCCN) Guidelines for B-cell Lymphoma, Central Nervous System Cancers, CLL/SLL, Hairy Cell Leukemia, Hematopoietic Cell Transplantation (HCT): Pre-Transplant Recipient Evaluation and Management of Graft-Versus-Host Disease, and Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma recommend ibrutinib for the following relapsed or refractory diseases when first-line treatment has failed: mantle cell lymphoma, various marginal zone lymphomas, certain diffuse large B-cell lymphomas (DLBCL), primary CNS lymphoma, certain post-transplant lymphoproliferative disorders, CLL/SLL, hairy cell leukemia, chronic GVHD, and Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma. The NCCN also recommends ibrutinib as a first-line therapy option for CLL/SLL with or without a del(17p) mutation, certain cases of mantle cell lymphoma (to limit the number of cycles of therapy with a R-hyper-CVAD regimen), primary CNS lymphoma (for patients unsuitable for or intolerant to high-dose methotrexate), and for Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma.

POSITION STATEMENT:

Comparative Effectiveness

The Food and Drug Administration has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of ibrutinib (Imbruvica) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("A", "B", "C", and "D"):

A. **ONE** of the following to support clinical use is met ("1", "2", or "3"):

1. **BOTH** of the following are met regarding FDA labeling or NCCN Compendium ("a" and "b"):
    a. **EITHER** of the following (indication and usage) ["i" or "ii"]:
        i. Member is diagnosed with a condition that is consistent with an indication listed in the ibrutinib FDA-approved prescribing information (or package insert) **AND** member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert)
        ii. Indication **AND** usage are recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation (see Table 1)
    b. **EITHER** of the following (diagnostic testing) ["i" or "ii"]:
        i. The requested indication requires genetic/specific diagnostic testing per the FDA labeling* or NCCN Compendium, **AND BOTH** of the following are met:
            - The genetic/specific diagnostic testing has been completed
            - The results of the testing indicate therapy is appropriate – documentation must be submitted
        ii. The requested indication does **NOT** require specific genetic/diagnostic testing per FDA labeling or NCCN Compendium

        **FDA Companion Diagnostics: https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools*
2. Ibrutinib is designated as an orphan drug by the FDA for the requested indication, **AND** the indication is not included in the FDA labeling or the NCCN compendium as a 1 or 2A recommendation (i.e., "Designated") [orphan drug designations can be found at http://www.accessdata.fda.gov/scripts/opdlisting/oopd/]
3. The indication and usage are supported by the results of **TWO** or more published clinical studies – the prescriber must submit full text copies of each article

    NOTE:

    - Case reports, posters, and abstracts (including published meeting abstracts) are **NOT** accepted as evidence to support use
    - Clinical studies must be supportive of use for a similar patient population (e.g., indication, diagnosis, disease severity, genetic or tumor mutations) and for the intended treatment plan, including any concomitant therapy

B. The dosage of ibrutinib not exceed the maximum FDA-approved dose and frequency with the following exceptions ("1" or "2"):

i. Dose and frequency for the indication are supported by standard reference compendia (see NCCN Compendium or other compendia in Table 2)

ii. Dose and frequency for the indication are supported by the results of **TWO** or more published clinical studies – the prescriber must submit full text copies of each article

NOTE: Dose ranging studies, case reports, posters, and abstracts (including published meeting abstracts) are not accepted as evidence to support use

C. The following tablet/capsule regimens must be used for the various solid oral dosages of ibrutinib:

- 70 mg once daily – one 70 mg capsule once daily
- 140 mg once daily – one 140 mg capsule once daily
- 280 mg once daily – two 140 mg capsules once daily
- 420 mg once daily –three140 mg capsules once daily
- 560 mg once daily – four 140 mg capsules once daily

D. Ibrutinib oral suspension is only permitted for use in the following scenarios ("1" or "2"):

1. Members under 12 years of age when the calculated dosage is based on body surface area (BSA). No more than two bottles (1 bottle = 108 mL of 70 mg/mL solution in a 150-mL container) are permitted per 30-day supply.
2. Members who are physically unable to swallow whole capsules. No more than two bottles (1 bottle = 108 mL of 70 mg/mL solution in a 150-mL container) are permitted per 30-day supply.

Duration of approval: 6 months

Continuation of ibrutinib (Imbruvica) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("A", "B", "C", and "D"):

A. Ibrutinib has been previously approved by Florida Blue or another health plan in the past 2 years, **OR** the member has previously met **ALL** indication-specific criteria

B. The dosage of ibrutinib does not exceed the maximum FDA-approved dose and frequency with the following exceptions:

b. Dose and frequency for the indication are supported by standard reference compendia (see NCCN Compendium or Table 2)

c. Dose and frequency for the indication are supported by the results of **TWO** or more published clinical studies – the prescriber must submit full text copies of each article

NOTE: Dose ranging studies, case reports, posters, and abstracts (including published meeting abstracts) are not accepted as evidence to support use

C. The following tablet/capsule regimens must be used for the various solid oral dosages of ibrutinib:

- 70 mg once daily – one 70 mg capsule once daily
- 140 mg once daily – one 140 mg capsule once daily
- 280 mg once daily – two 140 mg capsules once daily
- 420 mg once daily – three 140 mg capsules once daily
- 560 mg once daily - four 140 mg capsules once daily

D. Ibrutinib oral suspension is only permitted for use in the following scenarios ("1" or "2"):

1. Members under 12 years of age when the calculated dosage is based on body surface area (BSA). No more than two bottles (1 bottle = 108 mL of 70 mg/mL solution in a 150-mL container) are permitted per 30-day supply.

2. Members who are physically unable to swallow whole capsules. No more than two bottles (1 bottle = 108 mL of 70 mg/mL solution in a 150-mL container) are permitted per 30-day supply.

Duration of approval: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Chronic lymphocytic leukemia/ small lymphocytic lymphoma (with or without 17p deletion): 420 mg taken orally once daily. Can be administered as a single agent, in combination with rituximab or obinutuzumab, or in combination with bendamustine and rituximab (BR). When administering ibrutinib in combination with rituximab or obinutuzumab, consider administering ibrutinib prior to rituximab or obinutuzumab when given on the same day.
- Waldenström's macroglobulinemia: 420 mg taken orally once daily as a single-agent or in combination with rituximab until disease progression or unacceptable toxicity. Can be administered as a single agent or in combination with rituximab.
- Chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy (adult and pediatric patients age 1 year and older): 420 mg [for patients age 12 years and older] or 240 mg/m^2 (up to 420 mg) [for patients 1 to less than 12 years of age] taken orally once daily until cGVHD progression, recurrence of an underlying malignancy, or unacceptable toxicity. When a patient no longer requires therapy for the treatment of cGVHD, ibrutinib should be discontinued considering the medical assessment of the individual patient.

Dose Adjustments

Toxicity

- Interrupt ibrutinib therapy for any Grade 3 or greater non-hematological toxicities, Grade 2 cardiac failure, Grade 3 cardiac arrhythmias, Grade 3 or greater neutropenia with infection or fever, or Grade 4 hematological toxicities.
- Once the symptoms of the toxicity have resolved to Grade 1 or baseline (recovery), ibrutinib therapy may be reinitiated at reduce dose (reduced by 140 mg per day for patient 12 years and older or reduce to 160 mg/m^2 per day for patients 1 to 12 years of age with cGVHD).
- A second reduction of dose by 140 mg for patient 12 years and older (or reduce to 80 mg/m^2 per day for patients 1 to 12 years of age with cGVHD) (except for Grade 3 cardiac arrhythmias) may be considered as needed. If these toxicities persist or recur following two dose reductions, discontinue ibrutinib. Refer to the package insert for complete information.
- Permanently discontinue ibrutinib after the first occurrence of Grade 3 or 4 cardiac failure or Grade 4 cardiac arrhythmias.

Hepatic Impairment

- Adult Patients with B-cell Malignancies:

- For patients with mild liver impairment (Child-Pugh A), the recommended dose is 140 mg daily
- For patients with moderate hepatic impairment (Child-Pugh class B), the recommended dose is 70 mg daily
- Avoid the use in patients with severe hepatic impairment (Child-Pugh C).

- Patients with cGVHD:
  - The recommended dosage is 140 mg daily for patients 12 years of age and older with total bilirubin level >1.5 to 3-times upper limit of normal (ULN) (unless of non-hepatic origin or due to Gilbert's syndrome).
  - The recommended dosage is 80 mg/m^2 daily for patients 1 to less than 12 years of age with total bilirubin level >1.5 to 3-times ULN (unless of non-hepatic origin or due to Gilbert's syndrome).
  - Avoid the use in these patients with total bilirubin level >3-times ULN (unless of non-hepatic origin or due to Gilbert's syndrome)

Use with CYP3A Inhibitors

- A dose reduction or avoiding use of ibrutinib may be warranted for moderate or strong CYP3A4 inhibitors and depends on if use is for a B-cell malignancy or cGVHD. Refer to the product labeling for the specific recommendations. Specific dosage reductions are recommended for co-administration with voriconazole or posaconazole.

Drug Availability

- 70 mg capsule, 70 mg/mL oral suspension (supplied as 108 mL in a 150-mL bottle), 140 mg capsule, 140 mg tablet, 280 mg tablet, and 420 mg tablet.

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- None

Precautions/Warnings

- **Hemorrhage**: Monitor for bleeding. Ibrutinib may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies. Consider the benefit-risk of withholding treatment for at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.
- **Infections**: Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with therapy. Grade 3 or greater infections occurred in 21% of 1,476 patients who received ibrutinib in clinical trials. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. Monitor patients for fever and infections and evaluate promptly. Cases of progressive multifocal leukoencephalopathy (PML) have occurred.
- **Cytopenias**: In 645 patients with B-cell malignancies who received ibrutinib as a single agent, grade 3 or 4 neutropenia occurred in 23% of patients, grade 3 or 4 thrombocytopenia in 8% and grade 3 or 4 anemia in 3%, based on laboratory measurements. Check complete blood counts monthly.

- **Cardiac Arrhythmias, Cardiac Failure and Sudden Death:** Fatal and serious cardiac arrhythmias and cardiac failure have occurred. These adverse reactions occurred in patients with and without preexisting hypertension or cardiac comorbidities. Patients with cardiac comorbidities may be at greater risk of these events. Evaluate cardiac history and function at baseline and monitor patients for cardiac arrhythmias and cardiac function. Obtain further evaluation (e.g., ECG, echocardiogram) as indicated for patients who develop symptoms of arrhythmia (e.g., palpitations, lightheadedness, syncope, chest pain), new onset dyspnea, or other cardiovascular concerns. Manage cardiac arrhythmias and cardiac failure appropriately, follow dose modification guidelines, and consider the risks and benefits of continued treatment.
- **Hypertension**: Monitor blood pressure and treat as needed.
- **Tumor Lysis Syndrome (TLS)**: Monitor patients at risk for TLS (e.g., high tumor burden)
- **Second Primary Malignancies**: Other malignancies have occurred in patients, including skin cancers, and other carcinomas.
- **Hepatotoxicity, Including Drug-Induced Liver Injury**: Monitor hepatic function throughout treatment.
- **Embryo-Fetal Toxicity**: Can cause fetal harm. Advise women of the potential risk to a fetus and to avoid pregnancy while taking the drug.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J8999	Prescription drug, oral, chemotherapeutic, Not Otherwise Specified

ICD-10 Diagnosis Codes That Support Medical Necessity

C16.0 – C16.9	Malignant neoplasm of stomach
C25.0 – C25.2	Malignant neoplasm of head, body, or tail of pancreas
C25.3	Malignant neoplasm of pancreatic duct
C25.4	Malignant neoplasm of endocrine pancreas
C25.7 – C25.9	Malignant neoplasm of other parts of pancreas, overlapping sites of pancreas, or unspecified part of pancreas
C82.00 – C82.09	Follicular lymphoma grade I
C82.10 – C82.19	Follicular lymphoma grade II
C82.20 – C82.29	Follicular lymphoma grade III, unspecified
C82.30 – C82.39	Follicular lymphoma grade IIIa
C82.40 – C82.49	Follicular lymphoma grade IIIb
C82.60 – C82.69	Cutaneous follicle center lymphoma
C82.80 – C82.89	Other types of follicular lymphoma
C82.90 – C82.99	Follicular lymphoma, unspecified
C83.00	Small cell B-cell lymphoma unspecified site
C83.01	Small cell B-cell lymphoma, lymph nodes of head, face, and neck
C83.02	Small cell B-cell lymphoma, intrathoracic lymph nodes

C83.03	Small cell B-cell lymphoma, intra-abdominal lymph nodes
C83.04	Small cell B-cell lymphoma, lymph nodes of axilla and upper limb
C83.05	Small cell B-cell lymphoma, lymph nodes of inguinal region and lower limb
C83.06	Small cell B-cell lymphoma, intrapelvic lymph nodes
C83.07	Small cell B-cell lymphoma, spleen
C83.08	Small cell B-cell lymphoma, lymph nodes of multiple sites
C83.09	Small cell B-cell lymphoma, extranodal and solid organ sites
C83.10	Mantle cell lymphoma, unspecified site
C83.11	Mantle cell lymphoma, lymph nodes of head, face, and neck
C83.12	Mantle cell lymphoma, intrathoracic lymph nodes
C83.13	Mantle cell lymphoma, intra-abdominal lymph nodes
C83.14	Mantle cell lymphoma, lymph nodes of axilla and upper limb
C83.15	Mantle cell lymphoma, lymph nodes of inguinal region and lower limb
C83.16	Mantle cell lymphoma, intrapelvic lymph nodes
C83.17	Mantle cell lymphoma, spleen
C83.18	Mantle cell lymphoma, lymph nodes of multiple sites
C83.19	Mantle cell lymphoma, extranodal and solid organ sites
C83.30 – C83.398	Diffuse large B-cell lymphoma
C83.50	Lymphoblastic (diffuse) lymphoma, unspecified site
C83.51	Lymphoblastic (diffuse) lymphoma, lymph nodes of head, face, and neck
C83.52	Lymphoblastic (diffuse) lymphoma, intrathoracic lymph nodes
C83.53	Lymphoblastic (diffuse) lymphoma, intra-abdominal lymph nodes
C83.54	Lymphoblastic (diffuse) lymphoma, lymph nodes of axilla and upper limb
C83.55	Lymphoblastic (diffuse) lymphoma, lymph nodes of inguinal region and lower limb
C83.56	Lymphoblastic (diffuse) lymphoma, intrapelvic lymph nodes
C83.57	Lymphoblastic (diffuse) lymphoma, spleen
C83.58	Lymphoblastic (diffuse) lymphoma, lymph nodes of multiple sites
C83.80	Other non-follicular lymphoma, unspecified site
C83.81	Other non-follicular lymphoma, lymph nodes of head, face, and neck
C83.82	Other non-follicular lymphoma, intrathoracic lymph nodes
C83.83	Other non-follicular lymphoma, intra-abdominal lymph nodes
C83.84	Other non-follicular lymphoma, lymph nodes of axilla and upper limb
C83.85	Other non-follicular lymphoma, lymph nodes of inguinal region and lower limb
C83.86	Other non-follicular lymphoma, intrapelvic lymph nodes
C83.87	Other non-follicular lymphoma, spleen
C83.88	Other non-follicular lymphoma, lymph nodes of multiple sites
C83.89	Other non-follicular lymphoma, extranodal and solid organ sites
C83.90 – C83.99	Non-follicular (diffuse) lymphoma, unspecified
C85.20 – C85.29	Mediastinal (thymic) large B-cell lymphoma
C85.80 – C85.89	Other specified types of non-Hodgkin lymphoma
C85.99	Non-Hodgkin lymphoma, unspecified, extranodal and solid organ sites
C88.00	Waldenström's macroglobulinemia not having achieved remission

C88.08	Other lymphoplasmacytic lymphoma
C88.40	Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue [MALT-lymphoma] not having achieved remission
C90.00	Multiple myeloma not having achieved remission
C90.02	Multiple myeloma in relapse
C90.10	Plasma cell leukemia not having achieved remission
C90.12	Plasma cell leukemia in relapse
C91.10	Chronic lymphocytic leukemia of B-cell type, not having achieved remission
C91.11	Chronic lymphocytic leukemia of B-cell type, in remission
C91.12	Chronic lymphocytic leukemia of B-cell type, in relapse
C91.40	Hairy cell leukemia not having achieved remission
C91.42	Hairy cell leukemia in relapse
D47.Z1	Post-transplant lymphoproliferative disorder (PTLD)
D89.811	Chronic graft-versus-host disease
T86.09	Other complications of bone marrow transplant

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

Table 1

NCCN Categories of Evidence Consensus	
Category 1	Based upon high-level evidence; there is uniform NCCN consensus that the intervention is appropriate
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate

Category 2B	Based upon lower-level evidence, there NCCN consensus that the intervention is appropriate
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate

Table 2

Other Compendia	
Compendium	Covered Uses
AHFS-DI	Narrative text is supportive
Clinical Pharmacology	Narrative text is supportive
Lexicomp	Evidence rating A, B or G
Thomson Micromedex DrugDex	Meets requirements for BOTH of the following: Strength of recommendation: Class I (Recommended) or IIa (Recommended, In Most Cases) Efficacy: Class I (Effective) or IIa (Evidence Favors Efficacy)
AHFS-DI, American Hospital Formulary Service Drug Information	

Table 3

Lexicomp Recommendation Ratings	
A	Consistent evidence from well-performed randomized, controlled trials or overwhelming evidence of some other form (eg, results of the introduction of penicillin treatment) to support the off-label use. Further research is unlikely to change confidence in the estimate of benefit.
B	Evidence from randomized, controlled trials with important limitations (inconsistent results, methodological flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on confidence in the estimate of benefit and risk and may change the estimate.
C	Evidence from observational studies (eg, retrospective case series/reports providing significant impact on patient care), unsystematic clinical experience, or from potentially flawed randomized, controlled trials (eg, when limited options exist for condition). Any estimate of effect is uncertain.
G	Use has been substantiated by inclusion in at least one evidence-based or consensus-based clinical practice guideline.

Table 4

Thomson Micromedex DrugDex Recommendation Ratings: Strength of Recommendation		
Class I	Recommended	The given test or treatment has been proven to be useful, and should be performed or administered
Class IIa	Recommended, in most cases	The given test or treatment is generally considered to be useful and is indicated in most cases.

Class IIb	Recommended in some cases	The given test or treatment may be useful, and is indicated in some, but not most, cases
Class III	Not recommended	The given test or treatment is not useful and should be avoided
Class Indeterminate	Evidence Inconclusive	

Table 5

Thomson Micromedex DrugDex Recommendation Ratings: Efficacy		
Class I	Effective	Evidence and/or expert opinion suggests that a given drug treatment for a specific indication is effective
Class IIa	Evidence favors efficacy	Evidence and/or expert opinion is conflicting as to whether a given drug treatment for a specific indication is effective, but the weight of evidence and/or expert opinion favors efficacy.
Class IIb	Evidence is inconclusive	Evidence and/or expert opinion is conflicting as to whether a given drug treatment for a specific indication is effective, but the weight of evidence and/or expert opinion argues against efficacy.
Class III	Ineffective	Evidence and/or expert opinion suggests that a given drug treatment for a specific indication is ineffective

RELATED GUIDELINES:

Allogeneic Bone Marrow and Stem Cell Transplantation, 02-38240-01
Autologous Bone Marrow and Stem Cell Transplantation, 02-38241-01
Bendamustine HCl Injection, 09-J2000-40
Obinutuzumab (Gazyva), 09-J2000-07
Oral Oncology Medications, 09-J3000-65
Rituximab Products, 09-J0000-59

OTHER:

None

REFERENCES:

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 07/09/25.

GUIDELINE UPDATE INFORMATION:

03/15/14	New Medical Coverage Guideline.
04/15/14	Revision to guideline; consisting of description, position statement, dosing/administration, references.
10/15/14	Revision to guideline; consisting of position statement, coding
08/15/15	Review and revision to guideline; consisting of description, position statement, dosing/administration, references.
12/15/15	Revision to guideline consisting of updating the position statement and definitions section.
05/15/16	Revision to guideline consisting of updating the position statement based on expanded FDA indication and NCCN guideline updates, and updated references.
08/15/16	Review and revision to guideline consisting of updating the description section, position statement, dosing/administration section, billing/coding information, related guidelines, and references.
12/15/16	Revision to guideline consisting of updating the description section, position statement, and references based on updated NCCN guidelines for CLL/SLL.
05/15/17	Revision to guideline consisting of updating the description section, position statement, dosage/administration section, billing/coding information, and references based on a new FDA approved indication and updated NCCN guidelines for non-Hodgkin lymphomas.
08/15/17	Review and revision to guideline consisting of updating the description section, position statement, dosing/administration section, and references.
10/15/17	Revision to guideline consisting of updating the description section, position statement, dosage/administration section, billing/coding information, and references based on a new FDA approved indication for chronic Graft versus Host Disease (cGVHD).
04/15/18	Revision to guideline consisting of updating the description section, position statement, dosage/administration section, billing/coding information, and references based on new NCCN guideline recommendations for B-cell lymphomas and new tablet strengths.
08/15/18	Review and revision to guideline consisting of updating the description section, position statement, dosing/administration section, and references.
11/15/18	Revision to guideline consisting of updating the description section, position statement, and references based on revised NCCN guidelines for Waldenström's Macroglobulinemia.
03/15/19	Revision to guideline consisting of updating the description section, position statement, and references based on NCCN guideline updates and a new FDA-approved combination regimen with Gazyva for CLL/SLL.
08/15/19	Review and revision to guideline consisting of updating the description section, position statement, and references.
03/15/20	Revision to guideline consisting of updating the position statement regarding the use of capsules vs. tablets.
08/15/20	Review and revision to guideline consisting of updating the description section, position statement, related guidelines, and references.
08/15/21	Review and revision to guideline consisting of updating the position statement, warnings/precautions, related guidelines, billing/coding, and references.
08/15/22	Review and revision to guideline consisting of updating the description section, position statement, dosage/administration, precautions, definitions, and references.

10/15/22	Revision to guideline consisting of updating the description section, position statement, dosage /administration, and references based on the expanded indication of cGVHD to include patients 1 year of age and older and the new availability of an oral suspension.
07/01/23	Revision to guideline consisting of updating the description section, position statement, dosage/administration, and references due to the withdrawal of the accelerated approvals for mantle cell lymphoma and marginal zone lymphoma. The 560 mg tablet was discontinued. Quantity limit for the 140 mg capsule increased from three to four per day.
08/15/23	Review and revision to guideline consisting of updating the references.
08/15/24	Review and revision to guideline consisting of updating the description section, position statement, precautions, and references. A 560 mg strength must be obtained using four 140 mg capsules. Added an allowance for the oral suspension to be used for members (including adults) who are unable to swallow capsules. New precaution in the package labeling regarding hepatotoxicity, including drug-induced liver injury.
10/01/24	Revision: ICD-10 code updates.
08/15/25	Review and revision to guideline consisting of updating the references.