IMBRUVICA® (ibrutinib) is a once-daily oral therapy indicated for:

- Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)\(^1\)
- Chronic lymphocytic leukemia/small lymphocytic lymphoma with 17p deletion\(^1\)
- Waldenström’s macroglobulinemia (WM)\(^1\)
- Mantle cell lymphoma (MCL) patients who have received at least one prior therapy\(^1\)

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\(^1\)

**WARNINGS AND PRECAUTIONS**

Hemorrhage, infections, cytopenias, atrial fibrillation, hypertension, second primary malignancies, tumor lysis syndrome, embryo-fetal toxicity
IMBRUVICA® (ibrutinib) works differently than chemotherapy by inhibiting Bruton's tyrosine kinase (BTK)

- BTK is an important component of the BCR and cytokine receptor pathways, playing an essential role in regulating B-cell survival and proliferation.¹-⁴
- IMBRUVICA® is a small molecule that covalently binds to BTK, inhibiting BTK-dependent signaling pathways.⁵,⁶

Correlation of mechanism of action to clinical effect has not been established.

BCR B-cell receptor.
BTK Bruton's tyrosine kinase.
CD79A/B cluster of differentiation 79A/B adaptor molecules.
CXCR4/5 chemokine receptors 4/5 (C-X-C motif).
Cys481 cysteine 481.
DAG diacylglycerol.
IP3 inositol triphosphate.
Lyn tyrosine kinase.
MAPK mitogen-activated protein kinase.
NF-κB nuclear factor kappa-light-chain-enhancer of activated B cells.
PKCβ protein kinase C beta.
PLCγ2 phospholipase C gamma 2.
Syk spleen tyrosine kinase.

Please see the Important Safety Information on pages 10-11 and accompanying full Prescribing Information.
WARNINGS AND PRECAUTIONS

**Hemorrhage** - Fatal bleeding events have occurred in patients treated with IMBRUVICA®. Grade 3 or higher bleeding events (intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post-procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with IMBRUVICA®.

The mechanism for the bleeding events is not well understood. IMBRUVICA® may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding. Consider the benefit-risk of withholding IMBRUVICA® for at least 3 to 7 days pre- and postsurgery depending upon the type of surgery and the risk of bleeding.
IMBRUVICA® (ibrutinib) inhibits BTK to disrupt 3 key malignant B-cell processes (continued)

**WARNINGS AND PRECAUTIONS**

**Infections** - Fatal and nonfatal infections have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 14% to 29% of patients. Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis jirovecii* pneumonia (PJP) have occurred in patients treated with IMBRUVICA®. Evaluate patients for fever and infections and treat appropriately.

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**Inhibits adhesion**

- Adhesion molecules, which help keep B cells in proliferative microenvironments, are upregulated in certain B-cell malignancies. Adhesion molecules include:
  - ICAM-1
  - VCAM-1
  - ELAM-1

- IMBRUVICA® inhibits BTK and BCR-mediated adhesion, reducing malignant B-cell adhesion to connective tissue and stromal cells.

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**Key Processes**

**Inhibits adhesion**

- **Malignant B cells adhering to the microenvironment**
- **Malignant B cells released after IMBRUVICA® exposure**

**Key Components**

- FDC: follicular dendritic cell
- MSC: mesenchymal stromal cell
Modulates chemotaxis and trafficking*1,8,10,12,14-17

- IMBRUVICA® regulates B-cell migration in and out of lymphatic tissue14
- IMBRUVICA® inhibits BTK and cell migration by disrupting signaling pathways that regulate trafficking and chemotaxis8,10

*As demonstrated by in vitro and in vivo studies.
†Representative of microenvironments, such as the lymph nodes, spleen, and bone marrow, where malignant B cells can reside.
‡BTK inhibition leads to blockade of CXCR4/5 signaling in malignant B cells, which inhibits integrin-mediated adhesion. It is believed that the downregulation of BCR- and chemokine-induced adhesion leads to the compartmental shift of these malignant B cells from lymphoid tissues into peripheral blood.

Illustrations not to scale. Creative representation of simplified BTK signaling pathway and B-cell microenvironments.
Treatment-related lymphocytosis in IMBRUVICA® (ibrutinib) clinical trials

- Therapies that interfere with trafficking and adhesion of malignant cells by disrupting B-cell signaling can result in treatment-related lymphocytosis.\textsuperscript{18}
- Lymphocytosis is defined as ≥50% increase from baseline and above absolute lymphocyte count of 5,000/mcL\textsuperscript{1}
- Isolated asymptomatic lymphocytosis may be due to the mechanism of action of IMBRUVICA\textsuperscript{®} and may not be a sign of disease progression\textsuperscript{19,20}
- Lymphocytosis related to IMBRUVICA\textsuperscript{®} treatment generally resolved without dose reduction or discontinuation\textsuperscript{21}

![Image showing cell trafficking and adhesion]

Treatment-related lymphocytosis occurred in 66% of patients treated with single-agent IMBRUVICA\textsuperscript{®} across the CLL/SLL registration studies\textsuperscript{1}
- Onset occurs during the first month and resolves by a median of 14 weeks (range, 0.1 to 104 weeks)

Lymphocytosis occurred in 7% of patients treated with IMBRUVICA\textsuperscript{®} + BR vs 6% with placebo + BR\textsuperscript{1}

Treatment-related lymphocytosis occurred in 33% of patients in the MCL trial\textsuperscript{1}
- Onset occurs during the first few weeks and resolves by a median of 8 weeks
- MCL patients who develop lymphocytosis greater than 400,000/mcL have developed intracranial hemorrhage, lethargy, gait instability, and headache. However, some of these cases were in the setting of disease progression

Please see the Important Safety Information on pages 10-11 and accompanying full Prescribing Information.
Covalent binding of BTK by IMBRUVICA® provides sustained disruption of BTK-dependent signaling pathways

- IMBRUVICA® is absorbed after oral administration (median $T_{\text{max}}$ 1-2 hours), with a half-life of 4-6 hours$^1$
- IMBRUVICA® covalently binds to Cys481, a cysteine residue at the BTK active site$^{1,4}$
- IMBRUVICA® is metabolized in the liver primarily by cytochrome P450 (CYP3A)$^1$
- IMBRUVICA® is excreted primarily via feces, mainly in the form of metabolites$^1$
- IMBRUVICA® is not significantly cleared renally$^1$

**WARNINGS AND PRECAUTIONS**

**Cytopenias** - Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 13% to 29%), thrombocytopenia (range, 5% to 17%), and anemia (range, 0% to 13%) based on laboratory measurements occurred in patients treated with single agent IMBRUVICA®. Monitor complete blood counts monthly.

Please see the Important Safety Information on pages 10-11 and accompanying full Prescribing Information.
Oral, once-daily dosing

Continuous daily dosing of IMBRUVICA® (ibrutinib) is necessary to ensure inhibition of enzymatic activity.6,10,21

IMBRUVICA® single-agent dosing for CLL/SLL1

- 3 capsules (420 mg) ONCE DAILY
- Continue IMBRUVICA® treatment until disease progression or unacceptable toxicity

IMBRUVICA® + BR combination dosing for CLL/SLL1

- 3 capsules (420 mg) ONCE DAILY
- Continue IMBRUVICA® treatment until disease progression or unacceptable toxicity

• Bendamustine was dosed at 70 mg/m² and rituximab was dosed at 375 mg/m² and 500 mg/m²*

*For details on how IMBRUVICA® + BR was dosed and administered in previously treated CLL/SLL, please refer to the full IMBRUVICA® Prescribing Information (sections 2.2 and 14.2).

WARNINGS AND PRECAUTIONS

Atrial Fibrillation - Atrial fibrillation and atrial flutter (range, 6% to 9%) have occurred in patients treated with IMBRUVICA®, particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (eg, palpitations, lightheadedness) or new-onset dyspnea should have an ECG performed. Atrial fibrillation should be managed appropriately and if it persists, consider the risks and benefits of IMBRUVICA® treatment and follow dose modification guidelines.
IMBRUVICA® single-agent dosing for WM

**WM**

3 capsules (420 mg)
ONCE DAILY

Continue IMBRUVICA®
treatment until disease progression
or unacceptable toxicity

IMBRUVICA® single-agent dosing for MCL

**MCL**

4 capsules (560 mg)
ONCE DAILY

Continue IMBRUVICA®
treatment until disease progression
or unacceptable toxicity

**IMBRUVICA® administration**

- Swallow the capsules whole with water at approximately the same time each day
- Do not open, break, or chew the capsules
- If a patient misses a dose, tell patient to take IMBRUVICA® as soon as possible on the same day; patient returns to the regular schedule the next day. Tell patient not to take extra capsules to make up for the missed dose

For additional information on dosing, administration, and monitoring, please see the full Prescribing Information.
IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

**Hemorrhage** - Fatal bleeding events have occurred in patients treated with IMBRUVICA®. Grade 3 or higher bleeding events (intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post-procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with IMBRUVICA®.

The mechanism for the bleeding events is not well understood. IMBRUVICA® may increase the risk of hemorrhage in patients receiving antplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding. Consider the benefit-risk of withholding IMBRUVICA® 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 have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 14% to 29% of patients. Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis jirovecii* pneumonia (PJP) have occurred in patients treated with IMBRUVICA®. Evaluate patients for fever and infections and treat appropriately.

**Cytopenias** - Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 13% to 29%), thrombocytopenia (range, 5% to 17%), and anemia (range, 0% to 13%) based on laboratory measurements occurred in patients treated with single agent IMBRUVICA®. Monitor complete blood counts monthly.

**Atrial Fibrillation** - Atrial fibrillation and atrial flutter (range, 6% to 9%) have occurred in patients treated with IMBRUVICA®, particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (eg, palpitations, lightheadedness) or new-onset dyspnea should have an ECG performed. Atrial fibrillation should be managed appropriately and if it persists, consider the risks and benefits of IMBRUVICA® treatment and follow dose modification guidelines.

**Hypertension** - Hypertension (range, 6% to 17%) has occurred in patients treated with IMBRUVICA® with a median time to onset of 4.6 months (range, 0.03 to 22 months). Monitor patients for new-onset hypertension or hypertension that is not adequately controlled after starting IMBRUVICA®. Adjust existing antihypertensive medications and/or initiate antihypertensive treatment as appropriate.

**Second Primary Malignancies** - Other malignancies (range, 3% to 16%) including non-skin carcinomas (range, 1% to 4%) have occurred in patients treated with IMBRUVICA®. The most frequent second primary malignancy was non-melanoma skin cancer (range, 2% to 13%).

**Tumor Lysis Syndrome** - Tumor lysis syndrome has been infrequently reported with IMBRUVICA® therapy. Assess the baseline risk (e.g., high tumor burden) and take appropriate precautions. Monitor patients closely and treat as appropriate.

**Embryo-Fetal Toxicity** - Based on findings in animals, IMBRUVICA® can cause fetal harm when administered to a pregnant woman. Advise women to avoid becoming pregnant while taking IMBRUVICA® and for 1 month after cessation of therapy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Advise men to avoid fathering a child during the same time period.

**ADVERSE REACTIONS**

The most common adverse reactions (≥20%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia* (61%), thrombocytopenia* (62%), diarrhea (43%), anemia* (41%), musculoskeletal pain (30%), rash (30%), nausea (29%), bruising (30%), fatigue (29%), hemorrhage (22%), and pyrexia (21%).

*Based on adverse reactions and/or laboratory measurements (noted as platelets, neutrophils, or hemoglobin decreased).

The most common Grade 3 or 4 non-hematologic adverse reactions (≥5%) in MCL patients were pneumonia (7%), abdominal pain (5%), atrial fibrillation (5%), diarrhea (5%), fatigue (5%), and skin infections (5%).

The most common Grade 3 or 4 non-hematologic adverse reactions (≥5%) in MZL patients were pneumonia (10%), fatigue (6%), diarrhea (5%), rash (5%), and hypertension (5%).

Approximately 6% (CLL/SLL), 14% (MCL), 11% (WM) and 10% (MZL) of patients had a dose reduction due to adverse reactions. Approximately 4%-10% (CLL/SLL), 9% (MCL), and 9% (WM [6%] and MZL [13%]) of patients discontinued due to adverse reactions. Most frequent adverse reactions leading to discontinuation were pneumonia, hemorrhage, atrial fibrillation, rash, and neutropenia (1% each) in CLL/SLL patients and subdural hematoma (1.8%) in MCL patients. The most common adverse reactions leading to discontinuation were interstitial lung disease, diarrhea, and rash (1.6% each) in WM and MZL patients.

**DRUG INTERACTIONS**

**CYP3A Inhibitors** - Avoid coadministration with strong and moderate CYP3A inhibitors. If a moderate CYP3A inhibitor must be used, reduce the IMBRUVICA® dose.

**CYP3A Inducers** - Avoid coadministration with strong CYP3A inducers.

**SPECIFIC POPULATIONS**

**Hepatic Impairment** - Avoid use in patients with moderate or severe baseline hepatic impairment. In patients with mild impairment, reduce IMBRUVICA® dose.

Please see the accompanying full Prescribing Information.
IMBRUVICA®: THE FIRST-IN-CLASS COVALENT BTK INHIBITOR

Continuous BTK inhibition by IMBRUVICA® suppresses chronic B-cell proliferation by disrupting 3 key processes

1. Inhibits proliferation and survival\textsuperscript{1,8,9}
2. Inhibits adhesion\textsuperscript{10-12,14}
3. Modulates chemotaxis and trafficking\textsuperscript{8,10,14}

Please see the Important Safety Information on pages 10-11 and accompanying full Prescribing Information.