

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use IMBRUVICA safely and effectively. See full prescribing information for IMBRUVICA.

**IMBRUVICA® (ibrutinib) capsules, for oral use**  
**Initial U.S. Approval: 2013**

### RECENT MAJOR CHANGES

Indications and Usage (1.5, 1.6)	08/2017
Dosage and Administration (2.2, 2.3, 2.4, 2.5)	12/2017
Warnings and Precautions (5)	12/2017

### INDICATIONS AND USAGE

IMBRUVICA is a kinase inhibitor indicated for the treatment of adult patients with:

- Mantle cell lymphoma (MCL) who have received at least one prior therapy (1.1).  
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.
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL) (1.2).
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL) with 17p deletion (1.3).
- Waldenström's macroglobulinemia (WM) (1.4).
- Marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy (1.5).  
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.
- Chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy (1.6).

### DOSAGE AND ADMINISTRATION

- MCL and MZL: 560 mg taken orally once daily (four 140 mg capsules once daily) (2.2).
- CLL/SLL, WM, and cGVHD: 420 mg taken orally once daily (three 140 mg capsules once daily) (2.2).

Capsules should be taken orally with a glass of water. Do not open, break, or chew the capsules (2.1).

### DOSAGE FORMS AND STRENGTHS

Capsule: 70 mg and 140 mg (3)

## CONTRAINDICATIONS

None (4)

## WARNINGS AND PRECAUTIONS

- Hemorrhage: Monitor for bleeding and manage (5.1).
- Infections: Monitor patients for fever and infections, evaluate promptly, and treat (5.2).
- Cytopenias: Check complete blood counts monthly (5.3).
- Cardiac arrhythmias: Monitor for symptoms of arrhythmias and manage (5.4).
- Hypertension: Monitor blood pressure and treat (5.5).
- Second Primary Malignancies: Other malignancies have occurred in patients, including skin cancers, and other carcinomas (5.6).
- Tumor Lysis Syndrome (TLS): Assess baseline risk and take precautions. Monitor and treat for TLS (5.7).
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise women of the potential risk to a fetus and to avoid pregnancy while taking the drug and for 1 month after cessation of therapy. Advise men to avoid fathering a child during the same time period (5.8, 8.3).

## ADVERSE REACTIONS

The most common adverse reactions (≥20%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia, thrombocytopenia, diarrhea, anemia, musculoskeletal pain, rash, nausea, bruising, fatigue, hemorrhage, and pyrexia (6).

The most common adverse reactions (≥20%) in patients with cGVHD were fatigue, bruising, diarrhea, thrombocytopenia, muscle spasms, stomatitis, nausea, hemorrhage, anemia, and pneumonia (6).

**To report SUSPECTED ADVERSE REACTIONS, contact Pharmacovigilance at 1-877-877-3536 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

## DRUG INTERACTIONS

- CYP3A Inhibitors: Dose adjustments may be recommended (2.4, 7.1).
- CYP3A Inducers: Avoid coadministration with strong CYP3A inducers (7.2).

## USE IN SPECIFIC POPULATIONS

Hepatic Impairment (based on Child-Pugh criteria): Avoid use of IMBRUVICA in patients with severe baseline hepatic impairment. In patients with mild or moderate impairment, reduce IMBRUVICA dose (2.5, 8.6).

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling.

Revised: 12/2017

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

#### 1.1 Mantle Cell Lymphoma

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 [*see Clinical Studies (14.1)*].

#### 1.2 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

IMBRUVICA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) [*see Clinical Studies (14.2)*].

#### 1.3 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma with 17p deletion

IMBRUVICA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with 17p deletion [*see Clinical Studies (14.2)*].

#### 1.4 Waldenström's Macroglobulinemia

IMBRUVICA is indicated for the treatment of adult patients with Waldenström's macroglobulinemia (WM) [*see Clinical Studies (14.3)*].

#### 1.5 Marginal Zone Lymphoma

IMBRUVICA is indicated for the treatment of 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 [*see Clinical Studies (14.4)*]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

#### 1.6 Chronic Graft versus Host Disease

IMBRUVICA is indicated for the treatment of adult patients with chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy [*see Clinical Studies (14.5)*].

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Dosing Guidelines

Administer IMBRUVICA orally once daily at approximately the same time each day. Swallow the capsules whole with water. Do not open, break, or chew the capsules.

## 2.2 Recommended Dosage

### Mantle Cell Lymphoma and Marginal Zone Lymphoma

The recommended dose of IMBRUVICA for MCL and MZL is 560 mg (four 140 mg capsules) orally once daily until disease progression or unacceptable toxicity.

### Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma and Waldenström's Macroglobulinemia

The recommended dose of IMBRUVICA for CLL/SLL and WM is 420 mg (three 140 mg capsules) orally once daily until disease progression or unacceptable toxicity.

The recommended dose of IMBRUVICA for CLL/SLL when used in combination with bendamustine and rituximab (administered every 28 days for up to 6 cycles) is 420 mg (three 140 mg capsules) orally once daily until disease progression or unacceptable toxicity.

### Chronic Graft versus Host Disease

The recommended dose of IMBRUVICA for cGVHD is 420 mg (three 140 mg capsules) 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, IMBRUVICA should be discontinued considering the medical assessment of the individual patient.

## 2.3 Dose Modifications for Adverse Reactions

Interrupt IMBRUVICA therapy for any Grade 3 or greater non-hematological toxicities, 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), IMBRUVICA therapy may be reinitiated at the starting dose. If the toxicity reoccurs, reduce dose by one capsule (140 mg per day). A second reduction of dose by 140 mg may be considered as needed. If these toxicities persist or recur following two dose reductions, discontinue IMBRUVICA.

Recommended dose modifications are described below:

Toxicity Occurrence	Dose Modification for MCL and MZL After Recovery Starting Dose = 560 mg	Dose Modification for CLL/SLL, WM, and cGVHD After Recovery Starting Dose = 420 mg
First	Restart at 560 mg daily	Restart at 420 mg daily
Second	Restart at 420 mg daily	Restart at 280 mg daily
Third	Restart at 280 mg daily	Restart at 140 mg daily
Fourth	Discontinue IMBRUVICA	Discontinue IMBRUVICA

## 2.4 Dose Modifications for Use with CYP3A Inhibitors

Recommended dose modifications are described below [see *Drug Interactions (7.1)*]:

Patient Population	Coadministered Drug	Recommended IMBRUVICA Dose
B-Cell Malignancies	<ul style="list-style-type: none"> <li>Moderate CYP3A inhibitor</li> <li>Voriconazole 200 mg twice daily</li> <li>Posaconazole suspension 100 mg once daily, 100 mg twice daily, or 200 mg twice daily</li> </ul>	140 mg once daily Interrupt dose as recommended [see <i>Dosage and Administration (2.3)</i> ].
	<ul style="list-style-type: none"> <li>Posaconazole suspension 200 mg three times daily or 400 mg twice daily</li> <li>Posaconazole IV injection 300 mg once daily</li> <li>Posaconazole delayed-release tablets 300 mg once daily</li> </ul>	70 mg once daily Interrupt dose as recommended [see <i>Dosage and Administration (2.3)</i> ].
	<ul style="list-style-type: none"> <li>Other strong CYP3A inhibitors</li> </ul>	Avoid concomitant use. If these inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt IMBRUVICA.
Chronic Graft versus Host Disease	<ul style="list-style-type: none"> <li>Moderate CYP3A inhibitor</li> </ul>	420 mg once daily Modify dose as recommended [see <i>Dosage and Administration (2.3)</i> ].
	<ul style="list-style-type: none"> <li>Voriconazole 200 mg twice daily</li> <li>Posaconazole suspension 100 mg once daily, 100 mg twice daily, or 200 mg twice daily</li> </ul>	280 mg once daily Modify dose as recommended [see <i>Dosage and Administration (2.3)</i> ].
	<ul style="list-style-type: none"> <li>Posaconazole suspension 200 mg three times daily or 400 mg twice daily</li> <li>Posaconazole IV injection 300 mg once daily</li> <li>Posaconazole delayed-release tablets 300 mg once daily</li> </ul>	140 mg once daily Interrupt dose as recommended [see <i>Dosage and Administration (2.3)</i> ].
	<ul style="list-style-type: none"> <li>Other strong CYP3A inhibitors</li> </ul>	Avoid concomitant use. If these inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt IMBRUVICA.

After discontinuation of a CYP3A inhibitor, resume previous dose of IMBRUVICA [see *Dosage and Administration (2.2)* and *Drug Interactions (7.1)*].

## 2.5 Dose Modifications for Use in Hepatic Impairment

The recommended dose is 140 mg daily for patients with mild hepatic impairment (Child-Pugh class A).

The recommended dose is 70 mg daily for patients with moderate hepatic impairment (Child-Pugh class B).

Avoid the use of IMBRUVICA in patients with severe hepatic impairment (Child-Pugh class C) [see *Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*].

## 2.6 Missed Dose

If a dose of IMBRUVICA is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. Extra capsules of IMBRUVICA should not be taken to make up for the missed dose.

## 3 DOSAGE FORMS AND STRENGTHS

Capsule: 70 mg and 140 mg

## 4 CONTRAINDICATIONS

None

## 5 WARNINGS AND PRECAUTIONS

### 5.1 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 post-surgery depending upon the type of surgery and the risk of bleeding [see *Clinical Studies (14)*].

### 5.2 Infections

Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 14% to 29% of patients [see *Adverse Reactions (6.1, 6.2)*]. Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis jirovecii* pneumonia (PJP) have occurred in patients treated with IMBRUVICA. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. Monitor and evaluate patients for fever and infections and treat appropriately.

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