

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 (1.4)	01/15
Dosage and Administration (2.2, 2.3, 2.5)	01/15
Warnings and Precautions (5.1, 5.6)	01/15

INDICATIONS AND USAGE

IMBRUVICA is a kinase inhibitor indicated for the treatment of 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 of clinical benefit in confirmatory trials.
- Chronic lymphocytic leukemia (CLL) who have received at least one prior therapy (1.2).
- Chronic lymphocytic leukemia with 17p deletion (1.3).
- Waldenström's macroglobulinemia (WM) (1.4).

DOSAGE AND ADMINISTRATION

MCL: 560 mg taken orally once daily (four 140 mg capsules once daily) (2.2).
CLL and WM: 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: 140 mg (3)

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

- Hemorrhage: Monitor for bleeding (5.1).
- Infections: Monitor patients for fever and infections and evaluate promptly (5.2).
- Cytopenias: Check complete blood counts monthly (5.3).
- Atrial Fibrillation: Monitor patients for atrial fibrillation (5.4).
- Second Primary Malignancies: Other malignancies have occurred in patients, including skin cancers, and other carcinomas (5.5).
- Tumor Lysis Syndrome (TLS): Monitor patients at risk for TLS (e.g. high tumor burden) (5.6).
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise women of the potential risk to a fetus and to avoid pregnancy while taking the drug (5.7).

ADVERSE REACTIONS

The most common adverse reactions (≥25%) in patients with B-cell malignancies (MCL, CLL, WM) were thrombocytopenia, neutropenia, diarrhea, anemia, fatigue, musculoskeletal pain, bruising, nausea, upper respiratory tract infection, and rash.

To report SUSPECTED ADVERSE REACTIONS, contact Pharmacovigilance at 1-877-877-3536 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

CYP3A Inhibitors: Avoid co-administration with strong and moderate CYP3A inhibitors. If a moderate CYP3A inhibitor must be used, reduce IMBRUVICA dose (2.4, 7.1).

CYP3A Inducers: Avoid co-administration with strong CYP3A inducers (7.2).

USE IN SPECIFIC POPULATIONS

Hepatic Impairment: Avoid use of IMBRUVICA in patients with moderate or severe baseline hepatic impairment. In patients with mild impairment, reduce IMBRUVICA dose (8.7).

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

Revised: 01/2015

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Mantle Cell Lymphoma

IMBRUVICA is indicated for the treatment of 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 of clinical benefit in confirmatory trials [see *Clinical Studies (14.1)*].

1.2 Chronic Lymphocytic Leukemia

IMBRUVICA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy [see *Clinical Studies (14.2)*].

1.3 Chronic Lymphocytic Leukemia with 17p deletion

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

1.4 Waldenström's Macroglobulinemia

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

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 Dosage

Mantle Cell Lymphoma

The recommended dose of IMBRUVICA for MCL is 560 mg (four 140 mg capsules) orally once daily.

Chronic Lymphocytic Leukemia and Waldenström's Macroglobulinemia

The recommended dose of IMBRUVICA for CLL and WM is 420 mg (three 140 mg capsules) orally once daily.

2.3 Dose Modifications for Adverse Reactions

Interrupt IMBRUVICA therapy for any Grade 3 or greater non-hematological, 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	MCL Dose Modification After Recovery Starting Dose = 560 mg	CLL and WM Dose Modification 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

Avoid co-administration with strong or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition.

Concomitant use of strong CYP3A inhibitors which would be taken chronically (e.g., ritonavir, indinavir, nelfinavir, saquinavir, boceprevir, telaprevir, nefazodone) is not recommended. For short-term use (treatment for 7 days or less) of strong CYP3A inhibitors (e.g., antifungals and antibiotics) consider interrupting IMBRUVICA therapy until the CYP3A inhibitor is no longer needed [see *Drug Interactions (7.1)*].

Reduce IMBRUVICA dose to 140 mg if a moderate CYP3A inhibitor must be used (e.g., fluconazole, darunavir, erythromycin, diltiazem, atazanavir, aprepitant, amprenavir, fosamprevir, crizotinib, imatinib, verapamil, and ciprofloxacin) [see *Drug Interactions (7.1)*].

Patients taking concomitant strong or moderate CYP3A inhibitors should be monitored more closely for signs of IMBRUVICA toxicity.

2.5 Dose Modifications for Use in Hepatic Impairment

For patients with mild liver impairment (Child-Pugh class A), the recommended dose is 140 mg daily (one capsule). Avoid the use of IMBRUVICA in patients with moderate or severe hepatic impairment (Child-Pugh classes B and C) [see *Use in Specific Populations (8.7)* 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

140 mg capsules

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 (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.

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 have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 14% to 26% of patients. [*See Adverse Reactions (6.1)*]. Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with IMBRUVICA. Monitor patients for fever and infections and evaluate promptly.

5.3 Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 19 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 9%) occurred in patients treated with IMBRUVICA.

Monitor complete blood counts monthly.

5.4 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, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness) or new onset dyspnea should have an ECG performed. If atrial fibrillation persists, consider the risks and benefits of IMBRUVICA treatment and dose modification [*see Dosage and Administration (2.3)*].

5.5 Second Primary Malignancies

Other malignancies (range, 5 to 14%) including non-skin carcinomas (range, 1 to 3%) have occurred in patients treated with IMBRUVICA. The most frequent second primary malignancy was non-melanoma skin cancer (range, 4 to 11 %).

5.6 Tumor Lysis Syndrome

Tumor lysis syndrome has been reported with IMBRUVICA therapy. Monitor patients closely and take appropriate precautions in patients at risk for tumor lysis syndrome (e.g. high tumor burden).

5.7 Embryo-Fetal Toxicity

Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Ibrutinib caused malformations in rats at exposures 14 times those reported in patients with MCL and 20 times those reported in patients with CLL or WM, receiving the ibrutinib dose of 560 mg per day and 420 mg per day, respectively. Reduced fetal weights were observed at lower exposures. Advise women to avoid becoming pregnant while taking IMBRUVICA. 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 [see *Use in Specific Populations* (8.1)].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Hemorrhage [see *Warnings and Precautions* (5.1)]
- Infections [see *Warnings and Precautions* (5.2)]
- Cytopenias [see *Warnings and Precautions* (5.3)]
- Atrial Fibrillation [see *Warnings and Precautions* (5.4)]
- Second Primary Malignancies [see *Warnings and Precautions* (5.5)]
- Tumor Lysis Syndrome [see *Warnings and Precautions* (5.6)]

Because clinical trials are conducted under widely variable conditions, adverse event rates observed in clinical trials of a drug cannot be directly compared with rates of clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience

Mantle Cell Lymphoma

The data described below reflect exposure to IMBRUVICA in a clinical trial that included 111 patients with previously treated MCL treated with 560 mg daily with a median treatment duration of 8.3 months.

The most commonly occurring adverse reactions ($\geq 20\%$) were thrombocytopenia, diarrhea, neutropenia, anemia, fatigue, musculoskeletal pain, peripheral edema, upper respiratory tract infection, nausea, bruising, dyspnea, constipation, rash, abdominal pain, vomiting and decreased appetite (see [Tables 1 and 2](#)).

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