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 (1.2, 1.3)	5/2016
Dosage and Administration (2.2)	5/2016
Warnings and Precautions (5)	3/2016

---------------------------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)/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).

----------------------DOSAGE AND ADMINISTRATION----------------------

- MCL: 560 mg taken orally once daily (four 140 mg capsules once daily) (2.2).
- CLL/SLL 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 (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).
- Atrial Fibrillation: Monitor for atrial fibrillation 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, and WM) were neutropenia, thrombocytopenia, diarrhea, anemia, musculoskeletal pain, rash, nausea, bruising, fatigue, hemorrhage, and pyrexia (6).

To report SUSPECTED ADVERSE REACTIONS, contact Pharmacyclics 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 (based on Child-Pugh criteria): Avoid use of IMBRUVICA in patients with moderate or severe baseline hepatic impairment. In patients with mild impairment, reduce IMBRUVICA dose (2.5, 8.6).

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

Revised: 6/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
- 1.1 Mantle Cell Lymphoma
- 1.2 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
- 1.3 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma with 17p deletion
- 1.4 Waldenström's Macroglobulinemia

2 DOSAGE AND ADMINISTRATION
- 2.1 Dosing Guidelines
- 2.2 Dosage
- 2.3 Dose Modifications for Adverse Reactions
- 2.4 Dose Modifications for Use with CYP3A Inhibitors
- 2.5 Dose Modifications for Use in Hepatic Impairment
- 2.6 Missed Dose

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS
- 5.1 Hemorrhage
- 5.2 Infections
- 5.3 Cytopenias
- 5.4 Atrial Fibrillation
- 5.5 Hypertension
- 5.6 Second Primary Malignancies
- 5.7 Tumor Lysis Syndrome
- 5.8 Embryo-Fetal Toxicity

6 ADVERSE REACTIONS
- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS
- 7.1 CYP3A Inhibitors
- 7.2 CYP3A Inducers

8 USE IN SPECIFIC POPULATIONS
- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Hepatic Impairment
- 8.7 Plasmapheresis

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY
- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES
- 14.1 Mantle Cell Lymphoma
- 14.2 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
- 14.3 Waldenström's Macroglobulinemia

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

DOCKET ALARM

Find authenticated court documents without watermarks at docketalarm.com.

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/Small Lymphocytic Lymphoma

IMBRUVICA is indicated for the treatment of 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 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 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 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.

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

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	**MCL Dose Modification After Recovery** **Starting Dose = 560 mg**	**CLL/SLL 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 (8.6) and Clinical Pharmacology (12.3)]*.

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

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 (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 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) have occurred in patients treated with IMBRUVICA. Evaluate patients for fever and infections and treat appropriately.

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%) based on laboratory measurements occurred in patients treated with single agent 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, hypertension, acute infections,

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

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. Atrial fibrillation should be managed appropriately, and if it persists, consider the risks and benefits of IMBRUVICA treatment and follow dose modification guidelines *[see Dosage and Administration (2.3)]*.

5.5 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 anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

5.6 Second Primary Malignancies

Other malignancies (range, 5 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, 4 to 13%).

5.7 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.

5.8 Embryo-Fetal Toxicity

Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis caused embryofetal toxicity including malformations at exposures that were 2-20 times higher than those reported in patients with MCL, CLL/SLL or WM. 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 *[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)]*
- Hypertension *[see Warnings and Precautions (5.5)]*

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.

WHAT WILL YOU BUILD? | sales@docketalarm.com | 1-866-77-FASTCASE

fastcase®
Smarter legal research.