

**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**<sup>®</sup> (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 Pharmacyclics 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: 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

**FULL PRESCRIBING INFORMATION: CONTENTS\***

**1 INDICATIONS AND USAGE**

- 1.1 Mantle Cell Lymphoma
- 1.2 Chronic Lymphocytic Leukemia
- 1.3 Chronic Lymphocytic Leukemia 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 Second Primary Malignancies
- 5.6 Tumor Lysis Syndrome
- 5.7 Embryo-Fetal Toxicity

**6 ADVERSE REACTIONS**

- 6.1 Clinical Trials Experiences
- 6.2 Postmarketing Experience

**7 DRUG INTERACTIONS**

- 7.1 CYP3A Inhibitors
- 7.2 CYP3A Inducers

**8 USE IN SPECIFIC POPULATIONS**

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment
- 8.8 Females and Males of Reproductive Potential
- 8.9 Plasmapheresis

**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
- 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.

## 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](#)).

The most common Grade 3 or 4 non-hematological adverse reactions ( $\geq 5\%$ ) were pneumonia, abdominal pain, atrial fibrillation, diarrhea, fatigue, and skin infections.

Fatal and serious cases of renal failure have occurred with IMBRUVICA therapy. Increases in creatinine 1.5 to 3 times the upper limit of normal occurred in 9% of patients.

Adverse reactions from the MCL trial (N=111) using single agent IMBRUVICA 560 mg daily occurring at a rate of  $\geq 10\%$  are presented in [Table 1](#).

**Table 1: Non-Hematologic Adverse Reactions in  $\geq 10\%$  of Patients with  
MCL (N=111)**

<b>System Organ Class</b>	<b>Preferred Term</b>	<b>All Grades (%)</b>	<b>Grade 3 or 4 (%)</b>
<b>Gastrointestinal disorders</b>	Diarrhea	51	5
	Nausea	31	0
	Constipation	25	0
	Abdominal pain	24	5
	Vomiting	23	0
	Stomatitis	17	1
	Dyspepsia	11	0
<b>Infections and infestations</b>	Upper respiratory tract infection	34	0
	Urinary tract infection	14	3
	Pneumonia	14	7
	Skin infections	14	5
	Sinusitis	13	1
<b>General disorders and administrative site conditions</b>	Fatigue	41	5
	Peripheral edema	35	3
	Pyrexia	18	1
	Asthenia	14	3
<b>Skin and subcutaneous tissue disorders</b>	Bruising	30	0
	Rash	25	3
	Petechiae	11	0
<b>Musculoskeletal and connective tissue disorders</b>	Musculoskeletal pain	37	1
	Muscle spasms	14	0
	Arthralgia	11	0
<b>Respiratory, thoracic and mediastinal disorders</b>	Dyspnea	27	4
	Cough	19	0
	Epistaxis	11	0
<b>Metabolism and nutrition disorders</b>	Decreased appetite	21	2
	Dehydration	12	4
<b>Nervous system disorders</b>	Dizziness	14	0
	Headache	13	0

**Table 2: Treatment-Emergent\* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with MCL (N=111)**

	Percent of Patients (N=111)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	57	17
Neutrophils Decreased	47	29
Hemoglobin Decreased	41	9

\* Based on laboratory measurements and adverse reactions

Ten patients (9%) discontinued treatment due to adverse reactions in the trial (N=111). The most frequent adverse reaction leading to treatment discontinuation was subdural hematoma (1.8%). Adverse reactions leading to dose reduction occurred in 14% of patients.

Patients with MCL 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.

Forty percent of patients had elevated uric acid levels on study including 13% with values above 10 mg/dL. Adverse reaction of hyperuricemia was reported for 15% of patients.

### Chronic Lymphocytic Leukemia

The data described below reflect exposure to IMBRUVICA in an open label clinical trial (Study 1) that included 48 patients with previously treated CLL and a randomized clinical trial (Study 2) that included 391 randomized patients with previously treated CLL or SLL.

The most commonly occurring adverse reactions in Study 1 and Study 2 ( $\geq 20\%$ ) were thrombocytopenia, neutropenia, diarrhea, anemia, fatigue, musculoskeletal pain, upper respiratory tract infection, rash, nausea, and pyrexia.

Approximately five percent of patients receiving IMBRUVICA in Study 1 and Study 2 discontinued treatment due to adverse events. These included infections, subdural hematomas and diarrhea. Adverse events leading to dose reduction occurred in approximately 6% of patients.

### ***Study 1***

Adverse reactions and laboratory abnormalities from the CLL trial (N=48) using single agent IMBRUVICA 420 mg daily occurring at a rate of  $\geq 10\%$  are presented in [Tables 3](#) and [4](#).

**Table 3: Non-Hematologic Adverse Reactions in  $\geq 10\%$  of Patients with CLL (N=48) in Study 1**

System Organ Class	Preferred Term	All Grades (%)	Grade 3 or 4 (%)
<b>Gastrointestinal disorders</b>	Diarrhea	63	4
	Constipation	23	2
	Nausea	21	2
	Stomatitis	21	0
	Vomiting	19	2
	Abdominal pain	15	0
	Dyspepsia	13	0
<b>Infections and infestations</b>	Upper respiratory tract infection	48	2
	Sinusitis	21	6
	Skin infection	17	6
	Pneumonia	10	8
	Urinary tract infection	10	0
<b>General disorders and administrative site conditions</b>	Fatigue	31	4
	Pyrexia	25	2
	Peripheral edema	23	0
	Asthenia	13	4
	Chills	13	0
<b>Skin and subcutaneous tissue disorders</b>	Bruising	54	2
	Rash	27	0
	Petechiae	17	0
<b>Respiratory, thoracic and mediastinal disorders</b>	Cough	19	0
	Oropharyngeal pain	15	0
	Dyspnea	10	0
<b>Musculoskeletal and connective tissue disorders</b>	Musculoskeletal pain	27	6
	Arthralgia	23	0
	Muscle spasms	19	2
<b>Nervous system disorders</b>	Dizziness	21	0
	Headache	19	2
	Peripheral neuropathy	10	0
<b>Metabolism and nutrition disorders</b>	Decreased appetite	17	2
<b>Neoplasms benign, malignant, unspecified</b>	Second malignancies*	10*	0
<b>Injury, poisoning and procedural complications</b>	Laceration	10	2
<b>Psychiatric disorders</b>	Anxiety	10	0
	Insomnia	10	0
<b>Vascular disorders</b>	Hypertension	17	8

\*One patient death due to histiocytic sarcoma.

**Table 4: Treatment-Emergent\* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with CLL (N=48) in Study 1**

	Percent of Patients (N=48)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	71	10
Neutrophils Decreased	54	27
Hemoglobin Decreased	44	0

\* Based on laboratory measurements per IWCLL criteria and adverse reactions

### Study 2

Adverse reactions and laboratory abnormalities described below in Tables 5 and 6 reflect exposure to IMBRUVICA with a median duration of 8.6 months and exposure to ofatumumab with a median of 5.3 months in Study 2.

**Table 5: Non-Hematologic Adverse Reactions ≥ 10% Reported in Study 2**

System Organ Class ADR Term	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
<b>Gastrointestinal disorders</b>				
Diarrhea	48	4	18	2
Nausea	26	2	18	0
Stomatitis*	17	1	6	1
Constipation	15	0	9	0
Vomiting	14	0	6	1
<b>General disorders and administration site conditions</b>				
Fatigue	28	2	30	2
Pyrexia	24	2	15	1
<b>Infections and infestations</b>				
Upper respiratory tract infection	16	1	11	2
Pneumonia*	15	10	13	9
Sinusitis*	11	1	6	0
Urinary tract infection	10	4	5	1
<b>Skin and subcutaneous tissue disorders</b>				
Rash*	24	3	13	0
Petechiae	14	0	1	0
Bruising*	12	0	1	0

System Organ Class ADR Term	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
<b>Musculoskeletal and connective tissue disorders</b>				
Musculoskeletal Pain*	28	2	18	1
Arthralgia	17	1	7	0
<b>Nervous system disorders</b>				
Headache	14	1	6	0
Dizziness	11	0	5	0
<b>Injury, poisoning and procedural complications</b>				
Contusion	11	0	3	0
<b>Eye disorders</b>				
Vision blurred	10	0	3	0

Subjects with multiple events for a given ADR term are counted once only for each ADR term.

The system organ class and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

\* Includes multiple ADR terms

**Table 6: Treatment-Emergent\* Decrease of Hemoglobin, Platelets, or Neutrophils in Study 2**

	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Neutrophils Decreased	51	23	57	26
Platelets Decreased	52	5	45	10
Hemoglobin Decreased	36	0	21	0

\* Based on laboratory measurements per IWCLL criteria

### Waldenström's Macroglobulinemia

The data described below reflect exposure to IMBRUVICA in an open label clinical trial that included 63 patients with previously treated WM.

The most commonly occurring adverse reactions in the WM trial ( $\geq 20\%$ ) were neutropenia, thrombocytopenia, diarrhea, rash, nausea, muscle spasms, and fatigue.

Six percent of patients receiving IMBRUVICA in the WM trial discontinued treatment due to adverse events. Adverse events leading to dose reduction occurred in 11% of patients.

Adverse reactions and laboratory abnormalities described below in [Tables 7](#) and [8](#) reflect exposure to IMBRUVICA with a median duration of 11.7 months in the WM trial.

**Table 7: Non-Hematologic Adverse Reactions in  $\geq 10\%$  of Patients with Waldenström’s Macroglobulinemia (N=63)**

System Organ Class	Preferred Term	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	37	0
	Nausea	21	0
	Stomatitis*	16	0
	Gastroesophageal reflux disease	13	0
Skin and subcutaneous tissue disorders	Rash*	22	0
	Bruising*	16	0
	Pruritus	11	0
General disorders and administrative site conditions	Fatigue	21	0
Musculoskeletal and connective tissue disorders	Muscle spasms	21	0
	Arthropathy	13	0
Infections and infestations	Upper respiratory tract infection	19	0
	Sinusitis	19	0
	Pneumonia*	14	6
	Skin infection*	14	2
Respiratory, thoracic and mediastinal disorders	Epistaxis	19	0
	Cough	13	0
Nervous system disorders	Dizziness	14	0
	Headache	13	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	Skin cancer*	11	0

The system organ class and individual ADR terms are sorted in descending frequency order.

\* Includes multiple ADR terms.

**Table 8: Treatment-Emergent\* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with WM (N=63)**

	Percent of Patients (N=63)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	43	13
Neutrophils Decreased	44	19
Hemoglobin Decreased	13	8

\* Based on laboratory measurements.

## 6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of IMBRUVICA. Because these reactions are reported voluntarily from a population of uncertain size, it is not

always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity reactions including anaphylactic shock (fatal), urticaria, and angioedema have been reported.

## 7 DRUG INTERACTIONS

Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A.

### 7.1 CYP3A Inhibitors

In healthy volunteers, co-administration of ketoconazole, a strong CYP3A inhibitor, increased  $C_{max}$  and AUC of ibrutinib by 29- and 24-fold, respectively. The highest ibrutinib dose evaluated in clinical trials was 12.5 mg/kg (actual doses of 840 – 1400 mg) given for 28 days with single dose AUC values of  $1445 \pm 869$  ng · hr/mL which is approximately 50% greater than steady state exposures seen at the highest indicated dose (560 mg).

Avoid concomitant administration of IMBRUVICA with strong or moderate inhibitors of CYP3A. For strong CYP3A inhibitors used short-term (e.g., antifungals and antibiotics for 7 days or less, e.g., ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin) consider interrupting IMBRUVICA therapy during the duration of inhibitor use. Avoid strong CYP3A inhibitors that are needed chronically. If a moderate CYP3A inhibitor must be used, reduce the IMBRUVICA dose. Patients taking concomitant strong or moderate CYP3A4 inhibitors should be monitored more closely for signs of IMBRUVICA toxicity [*see Dosage and Administration (2.4)*].

Avoid grapefruit and Seville oranges during IMBRUVICA treatment, as these contain moderate inhibitors of CYP3A [*see Dosage and Administration (2.4), and Clinical Pharmacology (12.3)*].

### 7.2 CYP3A Inducers

Administration of IMBRUVICA with rifampin, a strong CYP3A inducer, decreased ibrutinib  $C_{max}$  and AUC by approximately 13- and 10-fold, respectively.

Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin and St. John's Wort). Consider alternative agents with less CYP3A induction [*see Clinical Pharmacology (12.3)*].

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category D [*see Warnings and Precautions (5.7)*].

*Risk Summary*

Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. If IMBRUVICA is used during pregnancy or if the patient becomes pregnant while taking IMBRUVICA, the patient should be apprised of the potential hazard to the fetus.

#### *Animal Data*

Ibrutinib was administered orally to pregnant rats during the period of organogenesis at oral doses of 10, 40 and 80 mg/kg/day. Ibrutinib at a dose of 80 mg/kg/day was associated with visceral malformations (heart and major vessels) and increased post-implantation loss. The dose of 80 mg/kg/day in animals is approximately 14 times the exposure (AUC) in patients with MCL and 20 times the exposure in patients with CLL or WM administered the dose of 560 mg daily and 420 mg daily, respectively. Ibrutinib at doses of 40 mg/kg/day or greater was associated with decreased fetal weights. The dose of 40 mg/kg/day in animals is approximately 6 times the exposure (AUC) in patients with MCL administered the dose of 560 mg daily.

### **8.3 Nursing Mothers**

It is not known whether ibrutinib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from IMBRUVICA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

### **8.4 Pediatric Use**

The safety and effectiveness of IMBRUVICA in pediatric patients has not been established.

### **8.5 Geriatric Use**

Of the 111 patients treated for MCL, 63% were 65 years of age or older. No overall differences in effectiveness were observed between these patients and younger patients. Cardiac adverse events (atrial fibrillation and hypertension), infections (pneumonia and cellulitis) and gastrointestinal events (diarrhea and dehydration) occurred more frequently among elderly patients.

Of the 391 patients randomized in Study 2, 61% were  $\geq 65$  years of age. No overall differences in effectiveness were observed between age groups. Grade 3 or higher adverse events occurred more frequently among elderly patients treated with IMBRUVICA (61% of patients age  $\geq 65$  versus 51% of younger patients) [see *Clinical Studies (14.2)*].

Of the 63 patients treated for WM, 59% were 65 years of age or older. No overall differences in effectiveness were observed between these patients and younger patients. Cardiac adverse events (atrial fibrillation and hypertension), and infections (pneumonia and urinary tract infection) occurred more frequently among elderly patients.

### **8.6 Renal Impairment**

Less than 1% of ibrutinib is excreted renally. Ibrutinib exposure is not altered in patients with Creatinine clearance (CLcr)  $> 25$  mL/min. There are no data in patients with severe renal impairment (CLcr  $< 25$  mL/min) or patients on dialysis [see *Clinical Pharmacology (12.3)*].

## 8.7 Hepatic Impairment

Ibrutinib is metabolized in the liver. In a hepatic impairment study, data showed an increase in ibrutinib exposure. Following single dose administration, the AUC of ibrutinib increased 2.7-, 8.2- and 9.8-fold in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function. The safety of IMBRUVICA has not been evaluated in patients with hepatic impairment.

Monitor patients for signs of IMBRUVICA toxicity and follow dose modification guidance as needed. It is not recommended to administer IMBRUVICA to patients with moderate or severe hepatic impairment (Child-Pugh classes B and C) [see *Dosage and Administration (2.5)* and *Clinical Pharmacology (12.3)*].

## 8.8 Females and Males of Reproductive Potential

Advise women to avoid becoming pregnant while taking IMBRUVICA because IMBRUVICA can cause fetal harm [see *Use in Specific Populations (8.1)*].

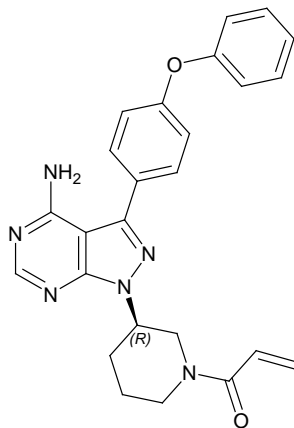
## 8.9 Plasmapheresis

Management of hyperviscosity in patients with WM may include plasmapheresis before and during treatment with IMBRUVICA. Modifications to IMBRUVICA dosing are not required.

## 11 DESCRIPTION

Ibrutinib is an inhibitor of Bruton's tyrosine kinase (BTK). It is a white to off-white solid with the empirical formula C<sub>25</sub>H<sub>24</sub>N<sub>6</sub>O<sub>2</sub> and a molecular weight 440.50. Ibrutinib is freely soluble in dimethyl sulfoxide, soluble in methanol and practically insoluble in water.

The chemical name for ibrutinib is 1-[(3*R*)-3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one and has the following structure:



IMBRUVICA (ibrutinib) capsules for oral administration are supplied as white opaque capsules that contain 140 mg ibrutinib as the active ingredient. Each capsule also contains the following inactive ingredients: croscarmellose sodium, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate. The capsule shell contains gelatin, titanium dioxide and black ink. Each white opaque capsule is marked with “ibr 140 mg” in black ink.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Ibrutinib is a small-molecule inhibitor of BTK. Ibrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. BTK's role in signaling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis, and adhesion. Nonclinical studies show that ibrutinib inhibits malignant B-cell proliferation and survival in vivo as well as cell migration and substrate adhesion in vitro.

### 12.2 Pharmacodynamics

In patients with recurrent B-cell lymphoma > 90% occupancy of the BTK active site in peripheral blood mononuclear cells was observed up to 24 hours after ibrutinib doses of  $\geq 2.5$  mg/kg/day ( $\geq 175$  mg/day for average weight of 70 kg).

### 12.3 Pharmacokinetics

#### Absorption

Ibrutinib is absorbed after oral administration with a median  $T_{max}$  of 1 to 2 hours. Ibrutinib exposure increases with doses up to 840 mg. The steady-state AUC (mean  $\pm$  standard deviation) observed in patients at 560 mg is  $953 \pm 705$  ng·h/mL and in patients at 420 mg is  $680 \pm 517$  ng·h/mL. Administration with food increased ibrutinib  $C_{max}$  and AUC by approximately 2 to 4- and 2-fold, respectively, compared with administration of ibrutinib after overnight fasting.

#### Distribution

Reversible binding of ibrutinib to human plasma protein in vitro was 97.3% with no concentration dependence in the range of 50 to 1000 ng/mL. The volume of distribution at steady state ( $V_{d,ss}$ ) was 683 L, and the apparent volume of distribution at steady state ( $V_{d,ss}/F$ ) was approximately 10000 L.

#### Metabolism

Metabolism is the main route of elimination for ibrutinib. It is metabolized to several metabolites primarily by cytochrome P450, CYP3A, and to a minor extent by CYP2D6. The active metabolite, PCI-45227, is a dihydrodiol metabolite with inhibitory activity towards BTK approximately 15 times lower than that of ibrutinib. The range of the mean metabolite to parent ratio for PCI-45227 at steady-state is 1 to 2.8.

#### Elimination

Intravenous clearance was 62 and 76 L/h in fasted and fed conditions, respectively. In line with the high first-pass effect, the apparent oral clearance is approximately 2000 and 1000 L/h in fasted and fed conditions, respectively. The half-life of ibrutinib is 4 to 6 hours.

Ibrutinib, mainly in the form of metabolites, is eliminated primarily via feces. After a single oral administration of radiolabeled [<sup>14</sup>C]-ibrutinib in healthy subjects, approximately 90% of radioactivity was excreted within 168 hours, with the majority (80%) excreted in the feces and less than 10% accounted for in urine. Unchanged ibrutinib accounted for approximately 1% of the radiolabeled excretion product in feces and none in urine, with the remainder of the dose being metabolites.

### **Age**

Age (37 to 84 years) does not alter ibrutinib systemic clearance.

### **Gender**

Gender does not alter ibrutinib systemic clearance.

### **Renal Impairment**

Ibrutinib is not significantly cleared renally; urinary excretion of metabolites is < 10% of the dose. Creatinine clearance > 25 mL/min had no influence on the exposure to IMBRUVICA. There are no data in patients with severe renal impairment (CL<sub>cr</sub> < 25 mL/min) or in patients on dialysis.

### **Hepatic Impairment**

Ibrutinib is metabolized in the liver. In a hepatic impairment trial, a single dose of 140 mg of IMBRUVICA was administered in non-cancer subjects. Ibrutinib AUC increased 2.7-, 8.2- and 9.8-fold, respectively, in subjects with mild (n=6), moderate (n=10) and severe (n=8) hepatic impairment relative to subjects with normal liver function. Ibrutinib C<sub>max</sub> increased 5.2-, 8.8- and 7.0-fold, respectively, in subjects with mild, moderate and severe hepatic impairment relative to subjects with normal liver function [*see Use in Specific Populations (8.7)*].

### **Drug Interactions**

#### *Coadministration of Ibrutinib with CYP3A Inhibitors*

In a sequential design trial of 18 healthy, fasted volunteers, a single dose of 120 mg of IMBRUVICA was administered alone on Day 1 and a single dose of 40 mg of IMBRUVICA was administered on Day 7 in combination with 400 mg of ketoconazole (given daily on Days 4 - 9). Ketoconazole increased ibrutinib dose-normalized C<sub>max</sub> and AUC 29-fold and 24-fold, respectively. Simulations using fasted conditions indicate that moderate CYP3A inhibitors diltiazem and erythromycin may increase AUC of ibrutinib by 5- to 8-fold.

#### *Coadministration of Ibrutinib with CYP3A Inducers*

PK data from a dedicated drug interaction trial showed that rifampin (a strong CYP3A inducer) decreases ibrutinib C<sub>max</sub> and AUC by more than 13- and 10-fold. Simulations using PBPK suggested that a moderate CYP3A inducer (efavirenz) may decrease the AUC of ibrutinib by up to 3-fold.

### *Coadministration of Ibrutinib with CYP Substrates*

In vitro studies indicated that ibrutinib ( $I/K_i < 0.07$  using mean  $C_{max}$  at 560 mg) and PCI-45227 ( $I/K_i < 0.03$ ) are unlikely to be inhibitors of any major CYPs at clinical doses. Both ibrutinib and the PCI-45227 are weak inducers of CYP450 isoenzymes in vitro.

### *Coadministration of Ibrutinib with Substrates of Transporters*

In vitro studies indicated that ibrutinib is not a substrate of p-glycoprotein (P-gp). Systemic ibrutinib is unlikely to be an inhibitor of P-gp at clinical doses ( $[I]_1/K_i < 0.1$ ). However, it may have an effect on P-gp substrates in the GI tract due to higher local concentrations after an oral dose. Co-administration of oral narrow therapeutic index P-gp substrates (e.g., digoxin) with IMBRUVICA may increase their blood concentration.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Carcinogenicity studies have not been conducted with ibrutinib.

Ibrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay, was not clastogenic in a chromosome aberration assay in mammalian (CHO) cells, nor was it clastogenic in an in vivo bone marrow micronucleus assay in mice at doses up to 2000 mg/kg.

Fertility studies with ibrutinib have not been conducted in animals. In the general toxicology studies conducted in rats and dogs, orally administered ibrutinib did not result in adverse effects on reproductive organs.

## **14 CLINICAL STUDIES**

### **14.1 Mantle Cell Lymphoma**

The safety and efficacy of IMBRUVICA in patients with MCL who have received at least one prior therapy were evaluated in an open-label, multi-center, single-arm trial of 111 previously treated patients. The median age was 68 years (range, 40 to 84 years), 77% were male, and 92% were Caucasian. At baseline, 89% of patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 42 months, and median number of prior treatments was 3 (range, 1 to 5 treatments), including 11% with prior stem cell transplant. At baseline, 39% of subjects had at least one tumor  $\geq 5$  cm, 49% had bone marrow involvement, and 54% had extranodal involvement at screening.

IMBRUVICA was administered orally at 560 mg once daily until disease progression or unacceptable toxicity. Tumor response was assessed according to the revised International Working Group (IWG) for non-Hodgkin's lymphoma (NHL) criteria. The primary endpoint in this study was investigator-assessed overall response rate (ORR). Responses to IMBRUVICA are shown in Table 9.

**Table 9: Overall Response Rate (ORR) and Duration of Response (DOR) Based on Investigator Assessment in Patients with MCL**

	<b>Total (N=111)</b>
ORR (%)	65.8
95% CI (%)	(56.2, 74.5)
CR (%)	17.1
PR (%)	48.6
Median DOR months (95% CI)	17.5 (15.8, NR)

CI = confidence interval; CR = complete response; PR = partial response; NR = not reached

An Independent Review Committee (IRC) performed independent reading and interpretation of imaging scans. The IRC review demonstrated an ORR of 69%.

The median time to response was 1.9 months.

### **Lymphocytosis**

Upon initiation of IMBRUVICA, a temporary increase in lymphocyte counts (i.e.,  $\geq 50\%$  increase from baseline and above absolute lymphocyte count of 5,000/mcL) occurred in 33% of patients in the MCL study. The onset of isolated lymphocytosis occurs during the first few weeks of IMBRUVICA therapy and resolves by a median of 8 weeks.

### **14.2 Chronic Lymphocytic Leukemia**

The safety and efficacy of IMBRUVICA in patients with CLL who have received at least one prior therapy were demonstrated in one uncontrolled trial and one randomized, controlled trial.

#### ***Study 1***

An open-label, multi-center trial was conducted in 48 previously treated CLL patients. The median age was 67 years (range, 37 to 82 years), 71% were male, and 94% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 80 months and the median number of prior treatments was 4 (range, 1 to 12 treatments). At baseline, 46% of subjects had at least one tumor  $\geq 5$  cm.

IMBRUVICA was administered orally at 420 mg once daily until disease progression or unacceptable toxicity. The ORR and DOR were assessed using a modified version of the International Workshop on CLL Criteria by an Independent Review Committee. The ORR was 58.3% (95% CI: 43.2%, 72.4%), all partial responses. None of the patients achieved a complete response. The DOR ranged from 5.6 to 24.2+ months. The median DOR was not reached.

#### ***Study 2***

A randomized, multicenter, open-label Phase 3 study of IMBRUVICA versus ofatumumab was conducted in patients with previously treated CLL or SLL. Patients (n=391) were randomized 1:1 to receive either IMBRUVICA 420 mg daily until disease progression, or unacceptable toxicity or ofatumumab at an initial dose of 300 mg, followed one week later by a dose of

2000 mg weekly for 7 doses and then every 4 weeks for 4 additional doses. Fifty seven patients randomized to ofatumumab crossed over following progression to receive IMBRUVICA. The median age was 67 years (range, 30 to 88 years), 68% were male, and 90% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. The trial enrolled 373 patients with CLL and 18 patients with SLL. The median time since diagnosis was 91 months and the median number of prior treatments was 2 (range, 1 to 13 treatments). At baseline, 58% of patients had at least one tumor  $\geq$  5 cm. Thirty-two percent of patients had 17p deletion.

Progression free survival (PFS) as assessed by independent review committee (IRC) according to IWCLL criteria indicated a 78% statistically significant reduction in the risk of death or progression. Analysis of overall survival (OS) demonstrated a 57% statistically significant reduction in the risk of death for patients in the IMBRUVICA arm. Efficacy results for Study 2 are shown in Table 10 and the Kaplan-Meier curves for PFS and OS are shown in [Figures 1 and 2](#), respectively.

**Table 10: Efficacy Results in Study 2**

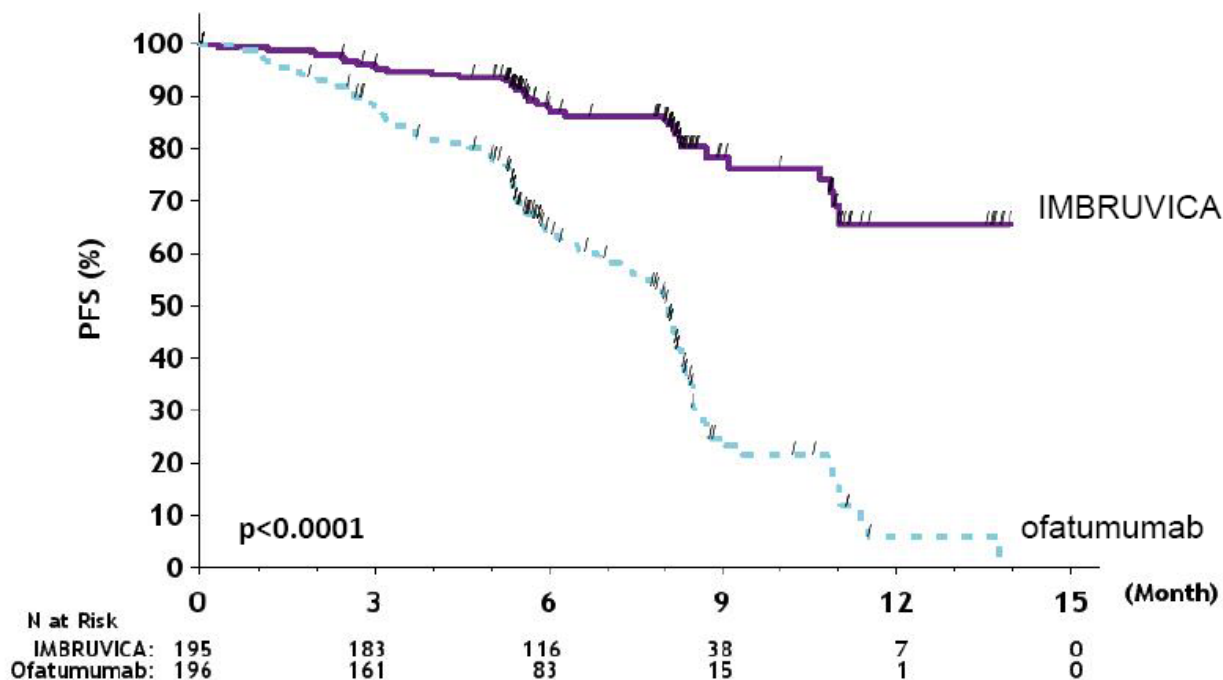
Endpoint	IMBRUVICA N=195	Ofatumumab N=196
<b>Progression Free Survival</b>		
Number of events (%)	35 (17.9)	111 (56.6)
Median (95% CI), months	Not reached	8.1 (7.2, 8.3)
HR (95% CI)	0.22 (0.15, 0.32)	
<b>Overall Survival<sup>a</sup></b>		
Number of death (%)	16 (8.2)	33 (16.8)
HR (95% CI)	0.43 (0.24, 0.79)	
Overall Response Rate <sup>b</sup>	42.6%	4.1%

<sup>a</sup> Median OS not reached for either arm

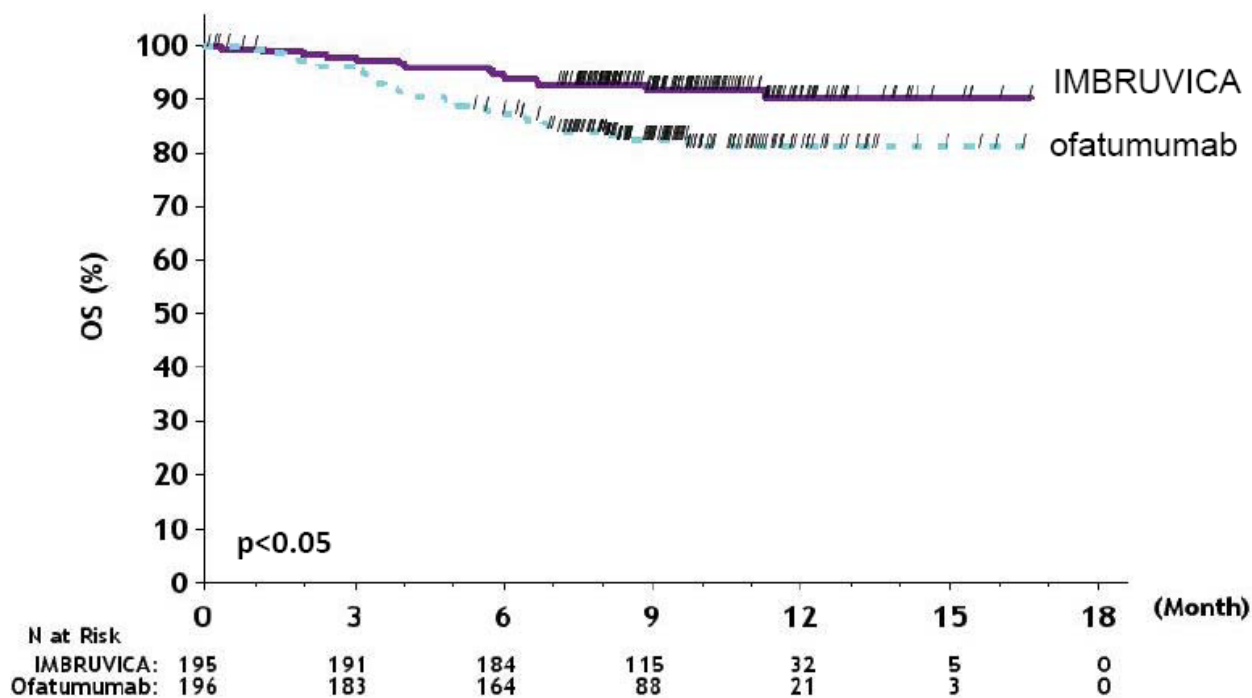
<sup>b</sup> IRC evaluated. All partial responses achieved; none of the patients achieved a complete response.

HR = hazard ratio

**Figure 1: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Study 2**



**Figure 2: Kaplan-Meier Curve of Overall Survival (ITT Population) in Study 2**



***CLL with 17p deletion (del 17p CLL)***

Study 2 included 127 patients with del 17p CLL. The median age was 67 years (range, 30 to 84 years), 62% were male, and 88% were Caucasian. All patients had a baseline ECOG

performance status of 0 or 1. PFS and ORR were assessed by IRC. Efficacy results for del 17p CLL are shown in Table 11.

**Table 11: Efficacy Results in Patients with del 17p CLL**

Endpoint	IMBRUVICA N=63	Ofatumumab N=64
<b>Progression Free Survival</b>		
Number of events (%)	16 (25.4)	38 (59.4)
Median (95% CI), months	Not reached	5.8 (5.3, 7.9)
HR (95% CI)	0.25 (0.14, 0.45)	
Overall Response Rate <sup>a</sup>	47.6%	4.7%

<sup>a</sup> IRC evaluated. All partial responses achieved; none of the patients achieved a complete response.  
HR = hazard ratio

### Lymphocytosis

Upon initiation of IMBRUVICA, an increase in lymphocyte counts (i.e.,  $\geq 50\%$  increase from baseline and above absolute lymphocyte count of 5,000/mcL) occurred in 77% of patients in the CLL study. The onset of isolated lymphocytosis occurs during the first month of IMBRUVICA therapy and resolves by a median of 23 weeks (range 1 – 104+ weeks).

### 14.3 Waldenström’s Macroglobulinemia

The safety and efficacy of IMBRUVICA in WM were evaluated in an open-label, multi-center, single-arm trial of 63 previously treated patients. The median age was 63 years (range, 44 to 86 years), 76% were male, and 95% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 74 months, and the median number of prior treatments was 2 (range, 1 to 11 treatments). At baseline, the median serum IgM value was 3.5 g/dL (range, 0.7 to 8.4 g/dL).

IMBRUVICA was administered orally at 420 mg once daily until disease progression or unacceptable toxicity. The responses were assessed by investigators and an Independent Review Committee (IRC) using criteria adopted from the International Workshop of Waldenström’s Macroglobulinemia. Responses, defined as partial response or better, per IRC are shown in Table 12.

**Table 12: Response Rate and Duration of Response Based on IRC Assessment in Patients with WM**

	Total (N=63)
Response rate (CR+VGPR+PR), (%)	61.9
95% CI (%)	(48.8, 73.9)
Complete Response (CR)	0
Very Good Partial Response (VGPR), (%)	11.1
Partial Response (PR), (%)	50.8

Median duration of response, months (range)	NR (2.8+, 18.8+)
---	------------------

CI = confidence interval; NR = not reached

The median time to response was 1.2 months (range: 0.7-13.4 months).

## 16 HOW SUPPLIED/STORAGE AND HANDLING

The white opaque 140 mg capsules marked with “ibr 140 mg” in black ink are available in white HDPE bottles with a child-resistant closure:

- 90 capsules per bottle: NDC 57962-140-09
- 120 capsules per bottle: NDC 57962-140-12

Store bottles at room temperature 20°C to 25°C (68°F to 77°F). Excursions are permitted between 15°C and 30°C (59°F to 86°F). Retain in original package until dispensing.

## 17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

- *Hemorrhage:*  
Inform patients of the possibility of bleeding, and to report any signs or symptoms (blood in stools or urine, prolonged or uncontrolled bleeding). Inform the patient that IMBRUVICA may need to be interrupted for medical or dental procedures [see *Warnings and Precautions (5.1)*].
- *Infections:*  
Inform patients of the possibility of serious infection, and to report any signs or symptoms (fever, chills, weakness, confusion) suggestive of infection [see *Warnings and Precautions (5.2)*].
- *Atrial Fibrillation:*  
Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, and chest discomfort [see *Warnings and Precautions (5.4)*].
- *Second primary malignancies:*  
Inform patients that other malignancies have occurred in patients who have been treated with IMBRUVICA, including skin cancers and other carcinomas [see *Warnings and Precautions (5.5)*].
- *Tumor lysis syndrome:*  
Inform patients of the potential risk of tumor lysis syndrome and report any signs and symptoms associated with this event to their healthcare provider for evaluation [see *Warnings and Precautions (5.6)*].

- *Embryo-fetal toxicity:*  
Advise women of the potential hazard to a fetus and to avoid becoming pregnant [*see Warnings and Precautions (5.7)*].
- Inform patients to take IMBRUVICA orally once daily according to their physician's instructions and that the capsules should be swallowed whole with a glass of water without being opened, broken, or chewed at approximately the same time each day [*see Dosage and Administration (2.1)*].
- Advise patients that in the event of a missed daily dose of IMBRUVICA, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Patients should not take extra capsules to make up the missed dose [*see Dosage and Administration (2.5)*].
- Advise patients of the common side effects associated with IMBRUVICA [*see Adverse Reactions (6)*]. Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.
- Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products [*see Drug Interactions (7)*].
- Advise patients that they may experience loose stools or diarrhea, and should contact their doctor if their diarrhea persists. Advise patients to maintain adequate hydration.

Active ingredient made in China.

Distributed and Marketed by:

Pharmacyclics, Inc.  
Sunnyvale, CA USA 94085  
and

Marketed by:

Janssen Biotech, Inc.  
Horsham, PA USA 19044

Patent <http://www.imbruvica.com>

IMBRUVICA<sup>®</sup> is a registered trademark owned by Pharmacyclics, Inc.

© Pharmacyclics, Inc. 2015

© Janssen Biotech, Inc. 2015

**Patient Information**  
**IMBRUVICA (im-BRU-vih-kuh)**  
(ibrutinib) capsules

**What is IMBRUVICA?**

IMBRUVICA is a prescription medicine used to treat people with:

- Mantle cell lymphoma (MCL) who have received at least one prior treatment
- Chronic lymphocytic leukemia (CLL) who have received at least one prior treatment
- Chronic lymphocytic leukemia (CLL) with 17p deletion
- Waldenstrom's macroglobulinemia (WM)

It is not known if IMBRUVICA is safe and effective in children.

**What should I tell my healthcare provider before taking IMBRUVICA?**

**Before you take IMBRUVICA, tell your healthcare provider about all of your medical conditions, including if you:**

- have had recent surgery or plan to have surgery. Your healthcare provider may stop IMBRUVICA for any planned medical, surgical, or dental procedure.
- have bleeding problems
- have or had heart rhythm problems, smoke, or have a medical condition that increases your risk of heart disease, such as high blood pressure, high cholesterol, or diabetes
- have an infection
- have liver problems
- are pregnant or plan to become pregnant. IMBRUVICA can harm your unborn baby. You should not become pregnant while taking IMBRUVICA.
- are breastfeeding or plan to breastfeed. You and your healthcare provider should decide if you will take IMBRUVICA or breastfeed. You should not do both.

**Tell your healthcare provider about all the medicines you take**, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking IMBRUVICA with certain other medicines may affect how IMBRUVICA works and can cause side effects.

**How should I take IMBRUVICA?**

- Take IMBRUVICA exactly as your healthcare provider tells you to take it.
- Take IMBRUVICA 1 time a day.
- Swallow IMBRUVICA capsules whole with a glass of water. Do not open, break, or chew IMBRUVICA capsules.
- Take IMBRUVICA at about the same time each day.
- If you miss a dose of IMBRUVICA take it as soon as you remember on the same day. Take your next dose of IMBRUVICA at your regular time on the next day. Do not take 2 doses of IMBRUVICA on the same day to make up for a missed dose.

**What should I avoid while taking IMBRUVICA?**

- You should not drink grapefruit juice, eat grapefruit, or eat Seville oranges (often used in marmalades) while you are taking IMBRUVICA. These products may increase the amount of IMBRUVICA in your blood.

**What are the possible side effects of IMBRUVICA?**

**IMBRUVICA may cause serious side effects, including:**

- **Bleeding problems** can happen during treatment with IMBRUVICA that can be serious and may lead to death. Tell your healthcare provider if you have any signs of bleeding, including: blood in your stools or black stools (looks like tar), pink or brown urine, unexpected bleeding or bleeding that is severe or that you cannot control, vomit blood or vomit looks like coffee grounds, cough up blood or blood clots, increased bruising, feel dizzy or weak, confusion, change in your speech, or a headache that lasts a long time. Your risk of bleeding may increase if you are also taking a blood thinner medicine.
- **Infections** can happen during treatment with IMBRUVICA. These infections can be serious and may lead to death. Tell your healthcare provider right away if you have fever, chills, weakness, confusion, or other signs or symptoms of an infection while taking IMBRUVICA.

- **Decrease in blood cell counts.** Decreased blood counts (white blood cells, platelets, and red blood cells) are common with IMBRUVICA, but can also be severe. Your healthcare provider should do monthly blood tests to check your blood counts.
- **Heart rhythm problems (atrial fibrillation and atrial flutter).** Heart rhythm problems have happened in people treated with IMBRUVICA, especially in people who have an increased risk for heart disease, have an infection, or who have had heart rhythm problems in the past. Tell your healthcare provider if you get any symptoms of heart rhythm problems, such as feeling as if your heart is beating fast and irregular, lightheadedness, dizziness, shortness of breath, chest discomfort, or you faint.
- **Second primary cancers.** New cancers have happened in people who have been treated with IMBRUVICA, including cancers of the skin or other organs.
- **Tumor lysis syndrome (TLS).** TLS is caused by the fast breakdown of cancer cells. TLS can cause kidney failure and the need for dialysis treatment, abnormal heart rhythm, seizure, and sometimes death. Your healthcare provider may do blood tests to check you for TLS.
- **Kidney problems.** Kidney failure and death have happened in people with MCL receiving IMBRUVICA treatment.

**The most common side effects of IMBRUVICA include:** diarrhea, tiredness, muscle and bone pain, bruising, nausea, upper respiratory tract infection, and rash.

**Diarrhea is a common side effect in people who take IMBRUVICA. Drink plenty of fluids during treatment with IMBRUVICA to help reduce your risk of losing too much fluid (dehydration) due to diarrhea. Tell your healthcare provider if you have diarrhea that does not go away.**

These are not all the possible side effects of IMBRUVICA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

#### **How should I store IMBRUVICA?**

- Store IMBRUVICA at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep IMBRUVICA in the original container with the lid tightly closed.

**Keep IMBRUVICA and all medicines out of the reach of children.**

#### **General information about the safe and effective use of IMBRUVICA**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use IMBRUVICA for a condition for which it was not prescribed. Do not give IMBRUVICA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about IMBRUVICA that is written for health professionals.

#### **What are the ingredients in IMBRUVICA?**

**Active ingredient:** ibrutinib

**Inactive ingredients:** croscarmellose sodium, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate. The capsule shell contains gelatin, titanium dioxide and black ink.

Distributed and Marketed by: Pharmacyclics, Inc. Sunnyvale, CA USA 94085 and

Marketed by: Janssen Biotech, Inc. Horsham, PA USA 19044 For more information call 1-877-877-3536.

© Pharmacyclics, Inc. 2015

© Janssen Biotech, Inc. 2015