

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).

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.

1.4 Waldenström's Macroglobulinemia

IMBRUVICA is indicated for the treatment of adult patients with Waldenström's macroglobulinemia (WM).

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.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Guidelines

Administer IMBRUVICA orally once daily at approximately the same time each day. The dose should be taken orally with a glass of water. Do not open, break, or chew the capsules. Do not cut, crush, or chew the tablets.

2.2 Recommended Dosage

Mantle Cell Lymphoma and Marginal Zone Lymphoma

The recommended dose of IMBRUVICA for MCL and MZL is 560 mg 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 as a single agent, in combination with rituximab for WM, or in combination with bendamustine and rituximab or with obinutuzumab for CLL/SLL is 420 mg orally once daily until disease progression or unacceptable toxicity.

When administering IMBRUVICA in combination with rituximab or obinutuzumab, consider administering IMBRUVICA prior to rituximab or obinutuzumab when given on the same day.

Chronic Graft versus Host Disease

The recommended dose of IMBRUVICA for cGVHD is 420 mg 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 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"> Moderate CYP3A inhibitor 	280 mg once daily Modify dose as recommended [<i>see Dosage and Administration (2.3)</i>].
	<ul style="list-style-type: none"> Voriconazole 200 mg twice daily Posaconazole suspension 100 mg once daily, 100 mg twice daily, or 200 mg twice daily 	140 mg once daily Modify dose as recommended [<i>see Dosage and Administration (2.3)</i>].
	<ul style="list-style-type: none"> Posaconazole suspension 200 mg three times daily or 400 mg twice daily Posaconazole IV injection 300 mg once daily Posaconazole delayed-release tablets 300 mg once daily 	70 mg once daily Interrupt dose as recommended [<i>see Dosage and Administration (2.3)</i>].
	<ul style="list-style-type: none"> Other strong CYP3A inhibitors 	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"> Moderate CYP3A inhibitor 	420 mg once daily Modify dose as recommended [<i>see Dosage and Administration (2.3)</i>].
	<ul style="list-style-type: none"> Voriconazole 200 mg twice daily Posaconazole suspension 100 mg once daily, 100 mg twice daily, or 200 mg twice daily 	280 mg once daily Modify dose as recommended [<i>see Dosage and Administration (2.3)</i>].
	<ul style="list-style-type: none"> Posaconazole suspension 200 mg three times daily or 400 mg twice daily Posaconazole IV injection 300 mg once daily Posaconazole delayed-release tablets 300 mg once daily 	140 mg once daily Interrupt dose as recommended [<i>see Dosage and Administration (2.3)</i>].
	<ul style="list-style-type: none"> Other strong CYP3A inhibitors 	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 doses of IMBRUVICA should not be taken to make up for the missed dose.

3 DOSAGE FORMS AND STRENGTHS

Capsules:

Each 70 mg capsule is a yellow, opaque capsule marked with “ibr 70 mg” in black ink.

Each 140 mg capsule is a white, opaque capsule marked with “ibr 140 mg” in black ink.

Tablets:

Each 140 mg tablet is a yellow green to green round tablet debossed with “ibr” on one side and “140” on the other side.

Each 280 mg tablet is a purple oblong tablet debossed with “ibr” on one side and “280” on the other side.

Each 420 mg tablet is a yellow green to green oblong tablet debossed with “ibr” on one side and “420” on the other side.

Each 560 mg tablet is a yellow to orange oblong tablet debossed with “ibr” on one side and “560” on the other side.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Hemorrhage

Fatal bleeding events have occurred in patients treated with IMBRUVICA. Major hemorrhage (\geq Grade 3, serious, or any central nervous system events; e.g., intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post procedural hemorrhage) have occurred in 4% of patients, with fatalities occurring in 0.4% of 2,838 patients exposed to IMBRUVICA in 27 clinical trials. Bleeding events of any grade, including bruising and petechiae, occurred in 39% of patients treated with IMBRUVICA.

The mechanism for the bleeding events is not well understood.

Use of either anticoagulant or antiplatelet agents concomitantly with IMBRUVICA increases the risk of major hemorrhage. In IMBRUVICA clinical trials, 3.1% of patients taking IMBRUVICA without antiplatelet or anticoagulant therapy experienced major hemorrhage. The addition of antiplatelet therapy with or without anticoagulant therapy increased this percentage to 4.4%, and the addition of anticoagulant therapy with or without antiplatelet therapy increased this percentage to 6.1%. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with IMBRUVICA. Monitor for signs and symptoms 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 24% of 1,124 patients exposed to IMBRUVICA in clinical trials [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.

5.3 Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (23%), thrombocytopenia (8%), and anemia (3%) based on laboratory measurements occurred in patients with B-cell malignancies treated with single agent IMBRUVICA.

Monitor complete blood counts monthly.

5.4 Cardiac Arrhythmias

Fatal and serious cardiac arrhythmias have occurred with IMBRUVICA therapy. Grade 3 or greater ventricular tachyarrhythmias occurred in 0.2% of patients, and Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4% of 1,124 patients exposed to IMBRUVICA in clinical trials. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias. See Additional Important Adverse Reactions (6.1).

Periodically monitor patients clinically for cardiac arrhythmias. Obtain an ECG for patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. Manage cardiac arrhythmias 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 of any grade occurred in 12% of 1,124 patients treated with IMBRUVICA in clinical trials. Grade 3 or greater hypertension occurred in 5% of patients with a median time to onset of 5.9 months (range, 0.03 to 24 months).

Monitor blood pressure in patients treated with IMBRUVICA and initiate or adjust anti-hypertensive medication throughout treatment with IMBRUVICA as appropriate.

5.6 Second Primary Malignancies

Other malignancies (10%) including non-skin carcinomas (4%) have occurred in 1,124 patients treated with IMBRUVICA in clinical trials. The most frequent second primary malignancy was non-melanoma skin cancer (6%).

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 embryo-fetal toxicity including malformations at exposures that were 2-20 times higher than those reported in patients with hematologic malignancies. 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 clinically significant 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)*]
- Cardiac Arrhythmias [*see Warnings and Precautions (5.4)*]
- Hypertension [*see Warnings and Precautions (5.5)*]
- Second Primary Malignancies [*see Warnings and Precautions (5.6)*]
- Tumor Lysis Syndrome [*see Warnings and Precautions (5.7)*]

6.1 Clinical Trials Experience

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.

Mantle Cell Lymphoma

The data described below reflect exposure to IMBRUVICA in a clinical trial (Study 1104) 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)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or Higher (%)
Gastrointestinal disorders	Diarrhea	51	5
	Nausea	31	0
	Constipation	25	0
	Abdominal pain	24	5
	Vomiting	23	0
	Stomatitis	17	1
	Dyspepsia	11	0
Infections and infestations	Upper respiratory tract infection	34	0
	Urinary tract infection	14	3
	Pneumonia	14	8 [†]
	Skin infections	14	5
	Sinusitis	13	1
General disorders and administration site conditions	Fatigue	41	5
	Peripheral edema	35	3
	Pyrexia	18	1
	Asthenia	14	3
Skin and subcutaneous tissue disorders	Bruising	30	0
	Rash	25	3
	Petechiae	11	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	37	1
	Muscle spasms	14	0

Body System	Adverse Reaction	All Grades (%)	Grade 3 or Higher (%)
	Arthralgia	11	0
Respiratory, thoracic and mediastinal disorders	Dyspnea	27	5 [†]
	Cough	19	0
	Epistaxis	11	0
Metabolism and nutrition disorders	Decreased appetite	21	2
	Dehydration	12	4
Nervous system disorders	Dizziness	14	0
	Headache	13	0

[†] Includes one event with a fatal outcome.

Table 2: Treatment-Emergent* Hematologic Laboratory Abnormalities 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

Treatment-emergent Grade 4 thrombocytopenia (6%) and neutropenia (13%) occurred in patients.

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/Small Lymphocytic Lymphoma

The data described below reflect exposure in one single-arm, open-label clinical trial (Study 1102) and four randomized controlled clinical trials (RESONATE, RESONATE-2, and HELIOS, and iLLUMINATE) in patients with CLL/SLL (n=1,506 total and n=781 patients exposed to IMBRUVICA). Patients with creatinine clearance (CrCl) \leq 30 mL/min, AST or ALT \geq 2.5 x ULN (upper limit of normal), or total bilirubin \geq 1.5x ULN (unless of non-hepatic origin) were excluded from these trials. Study 1102 included 51 patients with previously treated CLL/SLL, RESONATE included 386 randomized patients with previously treated CLL or SLL who received single agent IMBRUVICA or ofatumumab, RESONATE-2 included 267 randomized patients with treatment naïve-CLL or SLL who were 65 years or older and

Metabolism and nutrition disorders				
Hypokalemia	11	0	1	1

The body system and individual ADR preferred terms are sorted in descending frequency order.

* Includes multiple ADR terms.

† Includes one event with a fatal outcome.

Grade 3 or 4 infusion related reactions were observed in 1% of patients treated with IMBRUVICA + R.

Study 1121

Adverse reactions and laboratory abnormalities described below in [Tables 13](#) and [14](#) reflect exposure to IMBRUVICA with a median duration of 11.6 months in Study 1121.

Table 13: Non-Hematologic Adverse Reactions in $\geq 10\%$ in Patients with MZL in Study 1121 (N=63)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or Higher (%)
Gastrointestinal disorders	Diarrhea	43	5
	Nausea	25	0
	Dyspepsia	19	0
	Stomatitis*	17	2
	Abdominal pain	16	2
	Constipation	14	0
	Abdominal pain upper	13	0
	Vomiting	11	2
General disorders and administrative site conditions	Fatigue	44	6
	Peripheral edema	24	2
	Pyrexia	17	2
Skin and subcutaneous tissue disorders	Bruising *	41	0
	Rash*	29	5
	Pruritus	14	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain*	40	3
	Arthralgia	24	2
	Muscle spasms	19	3
Infections and infestations	Upper respiratory tract infection	21	0
	Sinusitis*	19	0
	Bronchitis	11	0
	Pneumonia*	11	10
Metabolism and nutrition disorders	Decreased appetite	16	2
	Hyperuricemia	16	0
	Hypoalbuminemia	14	0
	Hypokalemia	13	0
Vascular disorders	Hemorrhage*	30	2 [†]
	Hypertension*	14	5

Body System	Adverse Reaction	All Grades (%)	Grade 3 or Higher (%)
Respiratory, thoracic and mediastinal disorders	Cough	22	2
	Dyspnea	21	2
Nervous system disorders	Dizziness	19	0
	Headache	13	0
Psychiatric disorders	Anxiety	16	2

The body system and individual ADR preferred terms are sorted in descending frequency order.

* Includes multiple ADR terms.

† Includes one event with a fatal outcome.

Table 14: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with MZL in Study 1121 (N=63)

	Percent of Patients (N=63)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	49	6
Hemoglobin Decreased	43	13
Neutrophils Decreased	22	13

Treatment-emergent Grade 4 thrombocytopenia (3%) and neutropenia (6%) occurred in patients.

Chronic Graft versus Host Disease

The data described below reflect exposure to IMBRUVICA in an open-label clinical trial (Study 1129) that included 42 patients with cGVHD after failure of first line corticosteroid therapy and required additional therapy.

The most commonly occurring adverse reactions in the cGVHD trial ($\geq 20\%$) were fatigue, bruising, diarrhea, thrombocytopenia, stomatitis, muscle spasms, nausea, hemorrhage, anemia, and pneumonia. Atrial fibrillation occurred in one patient (2%) which was Grade 3.

Twenty-four percent of patients receiving IMBRUVICA in the cGVHD trial discontinued treatment due to adverse reactions. The most common adverse reactions leading to discontinuation were fatigue and pneumonia. Adverse reactions leading to dose reduction occurred in 26% of patients.

Adverse reactions and laboratory abnormalities described below in [Tables 15](#) and [16](#) reflect exposure to IMBRUVICA with a median duration of 4.4 months in the cGVHD trial.

Table 15: Non-Hematologic Adverse Reactions in $\geq 10\%$ of Patients with cGVHD (N=42)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or Higher (%)
General disorders and administration site conditions	Fatigue	57	12
	Pyrexia	17	5
	Edema peripheral	12	0

Skin and subcutaneous tissue disorders	Bruising*	40	0
	Rash*	12	0
Gastrointestinal disorders	Diarrhea	36	10
	Stomatitis*	29	2
	Nausea	26	0
	Constipation	12	0
Musculoskeletal and connective tissue disorders	Muscle spasms	29	2
	Musculoskeletal pain*	14	5
Vascular disorders	Hemorrhage*	26	0
Infections and infestations	Pneumonia*	21	14 [†]
	Upper respiratory tract infection	19	0
	Sepsis*	10	10
Nervous system disorders	Headache	17	5
Injury, poisoning and procedural complications	Fall	17	0
Respiratory, thoracic and mediastinal disorders	Cough	14	0
	Dyspnea	12	2
Metabolism and nutrition disorders	Hypokalemia	12	7

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

* Includes multiple ADR terms.

[†] Includes 2 events with a fatal outcome.

Table 16: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with cGVHD (N=42)

	Percent of Patients (N=42)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	33	0
Neutrophils Decreased	10	10
Hemoglobin Decreased	24	2

Treatment-emergent Grade 4 neutropenia occurred in 2% of patients.

Additional Important Adverse Reactions

Cardiac Arrhythmias

In randomized controlled trials (n=1605; median treatment duration of 14.8 months for 805 patients treated with IMBRUVICA and 5.6 months for 800 patients in the control arm), the incidence of ventricular tachyarrhythmias (ventricular extrasystoles, ventricular arrhythmias, ventricular fibrillation, ventricular flutter, and ventricular tachycardia) of any grade was 1.0% versus 0.5% and of Grade 3 or greater was 0.2% versus 0% in patients treated with IMBRUVICA compared to patients in the control arm. In addition, the incidence of atrial fibrillation and atrial flutter of any grade was 9% versus 1.4% and for Grade 3 or greater was 4.1% versus 0.4% in patients treated with IMBRUVICA compared to patients in the control arm.

Diarrhea

In randomized controlled trials (n=1605; median treatment duration of 14.8 months for 805 patients treated with IMBRUVICA and 5.6 months for 800 patients in the control arm), diarrhea of any grade occurred at a rate of 39% of patients treated with IMBRUVICA compared to 18% of patients in the control arm. Grade 3 diarrhea occurred in 3% versus 1% of IMBRUVICA-treated patients compared to the control arm, respectively. The median time to first onset was 21 days (range, 0 to 708) versus 46 days (range, 0 to 492) for any grade diarrhea and 117 days (range, 3 to 414) versus 194 days (range, 11 to 325) for Grade 3 diarrhea in IMBRUVICA-treated patients compared to the control arm, respectively. Of the patients who reported diarrhea, 85% versus 89% had complete resolution, and 15% versus 11% had not reported resolution at time of analysis in IMBRUVICA-treated patients compared to the control arm, respectively. The median time from onset to resolution in IMBRUVICA-treated subjects was 7 days (range, 1 to 655) versus 4 days (range, 1 to 367) for any grade diarrhea and 7 days (range, 1 to 78) versus 19 days (range, 1 to 56) for Grade 3 diarrhea in IMBRUVICA-treated subjects compared to the control arm, respectively. Less than 1% of subjects discontinued IMBRUVICA due to diarrhea compared with 0% in the control arm.

Visual Disturbance

In randomized controlled trials (n=1605; median treatment duration of 14.8 months for 805 patients treated with IMBRUVICA and 5.6 months for 800 patients in the control arm), blurred vision and decreased visual acuity of any grade occurred in 11% of patients treated with IMBRUVICA (10% Grade 1, 2% Grade 2, no Grade 3 or higher) compared to 6% in the control arm (6% Grade 1 and <1% Grade 2 and 3). The median time to first onset was 91 days (range, 0 to 617) versus 100 days (range, 2 to 477) in IMBRUVICA-treated patients compared to the control arm, respectively. Of the patients who reported visual disturbances, 60% versus 71% had complete resolution and 40% versus 29% had not reported resolution at the time of analysis in IMBRUVICA-treated patients compared to the control arm, respectively. The median time from onset to resolution was 37 days (range, 1 to 457) versus 26 days (range, 1 to 721) in IMBRUVICA-treated subjects compared to the control arm, respectively.

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.

- Hepatobiliary disorders: hepatic failure including acute and/or fatal events, hepatic cirrhosis
- Respiratory disorders: interstitial lung disease
- Metabolic and nutrition disorders: tumor lysis syndrome [see *Warnings & Precautions (5.7)*]

- Immune system disorders: anaphylactic shock, angioedema, urticaria
- Skin and subcutaneous tissue disorders: Stevens-Johnson Syndrome (SJS), onychoclasia, panniculitis
- Infections: hepatitis B reactivation
- Nervous system disorders: peripheral neuropathy

7 DRUG INTERACTIONS

7.1 Effect of CYP3A Inhibitors on Ibrutinib

The coadministration of IMBRUVICA with a strong or moderate CYP3A inhibitor may increase ibrutinib plasma concentrations [see *Clinical Pharmacology (12.3)*]. Increased ibrutinib concentrations may increase the risk of drug-related toxicity.

Dose modifications of IMBRUVICA are recommended when used concomitantly with posaconazole, voriconazole and moderate CYP3A inhibitors [see *Dosage and Administration (2.4)*].

Avoid concomitant use of other strong CYP3A inhibitors. Interrupt IMBRUVICA if these inhibitors will be used short-term (such as anti-infectives for seven days or less) [see *Dosage and Administration (2.4)*].

Avoid grapefruit and Seville oranges during IMBRUVICA treatment, as these contain strong or moderate inhibitors of CYP3A.

7.2 Effect of CYP3A Inducers on Ibrutinib

The coadministration of IMBRUVICA with strong CYP3A inducers may decrease ibrutinib concentrations. Avoid coadministration with strong CYP3A inducers [see *Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

IMBRUVICA, a kinase inhibitor, can cause fetal harm based on findings from animal studies. There are no available data on IMBRUVICA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In animal reproduction studies, administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis at exposures up to 2-20 times the clinical doses of 420-560 mg daily produced embryofetal toxicity including structural abnormalities (*see Data*). 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.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Ibrutinib was administered orally to pregnant rats during the period of organogenesis at 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 resorptions and post-implantation loss. The dose of 80 mg/kg/day in rats is approximately 14 times the exposure (AUC) in patients with MCL or MZL and 20 times the exposure in patients with CLL/SLL 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 rats is approximately 6 times the exposure (AUC) in patients with MCL administered the dose of 560 mg daily.

Ibrutinib was also administered orally to pregnant rabbits during the period of organogenesis at doses of 5, 15, and 45 mg/kg/day. Ibrutinib at a dose of 15 mg/kg/day or greater was associated with skeletal variations (fused sternbrae) and ibrutinib at a dose of 45 mg/kg/day was associated with increased resorptions and post-implantation loss. The dose of 15 mg/kg/day in rabbits is approximately 2.0 times the exposure (AUC) in patients with MCL and 2.8 times the exposure in patients with CLL/SLL or WM administered the dose of 560 and 420 mg daily, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of ibrutinib or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production.

The development and health benefits of breastfeeding should be considered along with the mother's clinical need for IMBRUVICA and any potential adverse effects on the breastfed child from IMBRUVICA or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Conduct pregnancy testing in females of reproductive potential prior to initiating IMBRUVICA therapy.

Contraception

Females

Advise females of reproductive potential to avoid pregnancy while taking IMBRUVICA and for up to 1 month after ending treatment. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus.

Males

Advise men to avoid fathering a child while receiving IMBRUVICA, and for 1 month following the last dose of IMBRUVICA.

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the 1,124 patients in clinical studies of IMBRUVICA, 64% were ≥ 65 years of age, while 23% were ≥ 75 years of age. No overall differences in effectiveness were observed between younger and older patients. Anemia (all grades), pneumonia (Grade 3 or higher), thrombocytopenia, hypertension, and atrial fibrillation occurred more frequently among older patients treated with IMBRUVICA.

8.6 Hepatic Impairment

Avoid use of IMBRUVICA in patients with severe hepatic impairment (Child-Pugh class C). The safety of IMBRUVICA has not been evaluated in patients with mild to severe hepatic impairment by Child-Pugh criteria.

Dose modifications of IMBRUVICA are recommended in patients with mild or moderate hepatic impairment (Child-Pugh class A and B). Monitor patients for adverse reactions of IMBRUVICA closely [*see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)*].

8.7 Plasmapheresis

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

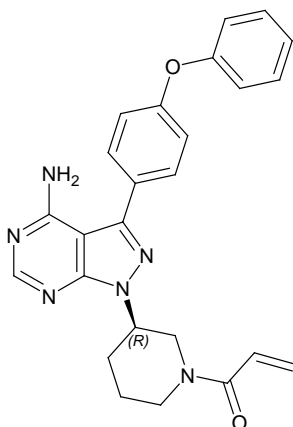
10 OVERDOSAGE

There is no specific experience in the management of ibrutinib overdose in patients. One healthy subject experienced reversible Grade 4 hepatic enzyme increases (AST and ALT) after a dose of 1680 mg. Closely monitor patients who ingest more than the recommended dosage and provide appropriate supportive treatment.

11 DESCRIPTION

Ibrutinib is an inhibitor of Bruton's tyrosine kinase (BTK). It is a white to off-white solid with the empirical formula $C_{25}H_{24}N_6O_2$ 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) is available as immediate-release oral capsules and immediate-release oral tablets.

IMBRUVICA (ibrutinib) capsules for oral administration are available in the following dosage strengths: 70 mg and 140 mg. Each capsule contains ibrutinib (active ingredient) and the following inactive ingredients: croscarmellose sodium, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate. The capsule shell contains gelatin, titanium dioxide, yellow iron oxide (70 mg capsule only), and black ink.

IMBRUVICA (ibrutinib) tablets for oral administration are available in the following dosage strengths: 140 mg, 280 mg, 420 mg, and 560 mg. Each tablet contains ibrutinib (active ingredient) and the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium lauryl sulfate. The film coating for each tablet contains ferrousferrous oxide (140 mg, 280 mg, and 420 mg tablets), polyvinyl alcohol, polyethylene glycol, red iron oxide (280 mg and 560 mg tablets), talc, titanium dioxide, and yellow iron oxide (140 mg, 420 mg, and 560 mg tablets).

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 ≥ 2.5 mg/kg/day (≥ 175 mg/day for average weight of 70 kg).

In vitro Platelet Aggregation

Ibrutinib demonstrated inhibition of collagen-induced platelet aggregation, with IC₅₀ values at 4.6 μ M (2026 ng/mL), 0.8 μ M (352 ng/mL), and 3 μ M (1321 ng/mL) in blood samples from healthy donors, donors taking warfarin, and donors with severe renal dysfunction, respectively. Ibrutinib did not show meaningful inhibition of platelet aggregation for ADP, arachidonic acid, ristocetin, and TRAP-6.

Cardiac Electrophysiology

At a single dose 3 times the maximum recommended dose (1680 mg), IMBRUVICA did not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

Ibrutinib exposure increases with doses up to 840 mg (1.5 times the maximum approved recommended dosage) in patients with B-cell malignancies. The mean steady-state AUC (% coefficient of variation) observed in patients at 560 mg with MCL is 865 (69%) ng·h/mL and with MZL is 978 (82%) ng·h/mL, and in patients at 420 mg with CLL/SLL is 708 (71%) ng·h/mL, with WM is 707 (72%) ng·h/mL, and with cGVHD is 1159 (50%) ng·h/mL. Steady-state concentrations of ibrutinib without CYP3A inhibitors were achieved with an accumulation ratio of 1 to 1.6 after 1 week of multiple daily doses of 420 mg or 560 mg.

Absorption

Absolute bioavailability of ibrutinib in fasted condition was 2.9% (90% CI: 2.1, 3.9) in healthy subjects. Ibrutinib is absorbed after oral administration with a median T_{max} of 1 hour to 2 hours.

Effect of Food

The administration of IMBRUVICA with a high-fat and high-calorie meal (800 calories to 1,000 calories with approximately 50% of total caloric content of the meal from fat) increased ibrutinib C_{max} by 2- to 4-fold and AUC by approximately 2-fold, compared with administration of ibrutinib after overnight fasting.

In vitro studies suggest that ibrutinib is not a substrate of p-glycoprotein (P-gp) or breast cancer resistance protein (BCRP).

Distribution

Reversible binding of ibrutinib to human plasma protein *in vitro* was 97.3% with no concentration dependence in the range of 50 ng/mL to 1000 ng/mL. The volume of distribution (V_d) was 683 L, and the apparent volume of distribution at steady state (V_{d,ss}/F) was approximately 10,000 L.

Elimination

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

Metabolism

Metabolism is the main route of elimination for ibrutinib. It is metabolized to several metabolites primarily by cytochrome P450 (CYP) 3A 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.

Excretion

Ibrutinib, mainly in the form of metabolites, is eliminated primarily via feces. After a single oral administration of radiolabeled ibrutinib, 90% of radioactivity was excreted within 168 hours, with 80% excreted in the feces and less than 10% eliminated in urine. Unchanged ibrutinib accounted for 1% of the radiolabeled excreted dose in feces and none in urine, with the remainder of the excreted dose being metabolites.

Specific Populations

Age and Sex

Age and sex have no clinically meaningful effect on ibrutinib pharmacokinetics.

Patients with Renal Impairment

Mild and moderate renal impairment (creatinine clearance [CL_{cr}] > 25 mL/min as estimated by Cockcroft-Gault equation) had no influence on the exposure of ibrutinib. No data is available in patients with severe renal impairment (CL_{cr} < 25 mL/min) or in patients on dialysis.

Patients with Hepatic Impairment

The AUC of ibrutinib increased 2.7-fold in subjects with mild hepatic impairment (Child-Pugh class A), 8.2-fold in subjects with moderate hepatic impairment (Child-Pugh class B) and 9.8-fold in subjects with severe hepatic impairment (Child-Pugh class C) relative to subjects with normal liver function. The C_{max} of ibrutinib increased 5.2-fold in mild hepatic impairment, 8.8-fold in moderate hepatic impairment and 7-fold in severe hepatic impairment relative to subjects with normal liver function [see *Use in Specific Populations (8.6)*].

Drug Interaction Studies

Effect of CYP3A Inhibitors on Ibrutinib

The coadministration of multiple doses of ketoconazole (strong CYP3A inhibitor) increased the C_{max} of ibrutinib by 29-fold and AUC by 24-fold. The coadministration of multiple doses of voriconazole (strong CYP3A inhibitor) increased steady state C_{max} of ibrutinib by 6.7-fold and

AUC by 5.7-fold. Simulations under fed conditions suggest that posaconazole (strong CYP3A inhibitor) may increase the AUC of ibrutinib 3-fold to 10-fold.

The coadministration of multiple doses of erythromycin (moderate CYP3A inhibitor) increased steady state C_{max} of ibrutinib by 3.4-fold and AUC by 3-fold.

Effect of CYP3A Inducers on Ibrutinib

The coadministration of rifampin (strong CYP3A inducer) decreased the C_{max} of ibrutinib by more than 13-fold and AUC by more than 10-fold. Simulations suggest that efavirenz (moderate CYP3A inducer) may decrease the AUC of ibrutinib by 3-fold.

Effect of Ibrutinib on CYP Substrates

In vitro studies suggest that ibrutinib and PCI-45227 are unlikely to inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A at clinical doses. Both ibrutinib and PCI-45227 are unlikely to induce CYP1A2, CYP2B6 or CYP3A at clinical doses.

Effect of Ibrutinib on Substrates of Transporters

In vitro studies suggest that ibrutinib may inhibit BCRP and P-gp transport at clinical doses. The coadministration of oral P-gp or BCRP substrates with a narrow therapeutic index (e.g., digoxin, methotrexate) with IMBRUVICA may increase their concentrations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Ibrutinib was not carcinogenic in a 6-month rasH2 mouse study at oral doses up to 2000 mg/kg/day resulting in exposures approximately 23 (males) to 37 (females) times higher than the exposure in humans at a dose of 560 mg daily [see *Warnings and Precautions* (5.6)].

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.

Rats were administered oral daily doses of ibrutinib for 4 weeks prior to pairing and during pairing in males and 2 weeks prior to pairing and during pairing in females. Treatment of female rats continued following pregnancy up to gestation day (GD) 7, and treatment of male rats continued until end of study. No effects on fertility or reproductive capacities were observed in male or female rats up to the maximum dose tested, 100 mg/kg/day (Human Equivalent Dose [HED] 16 mg/kg).

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 Study PCYC-1104-CA (referred to as Study 1104) (NCT01236391), 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 transplantation. 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 17](#).

Table 17: Overall Response Rate (ORR) and Duration of Response (DOR) Based on Investigator Assessment in Patients with MCL in Study 1104

	Total (N=111)
ORR (%)	65.8
95% CI (%)	(56.2, 74.5)
CR (%)	17.1
PR (%)	48.6
Median DOR months (95% CI)	17.5 (15.8, NE)

CI = confidence interval; CR = complete response; PR = partial response; NE = not evaluable

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 / Small Lymphocytic Lymphoma

The safety and efficacy of IMBRUVICA in patients with CLL/SLL were demonstrated in one uncontrolled trial and four randomized, controlled trials.

Study 1102

Study PCYC-1102-CA (referred to as Study 1102) (NCT01105247), 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.

RESONATE

The RESONATE study (A Randomized, Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor Ibrutinib versus Ofatumumab in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma) (NCT01578707) 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.

Efficacy results for RESONATE are shown in [Table 18](#) and the Kaplan-Meier curves for PFS, assessed by an IRC according to IWCLL criteria, and OS are shown in [Figures 1](#) and [2](#), respectively.

Table 18: Efficacy Results in Patients with CLL/SLL in RESONATE

Endpoint	IMBRUVICA N=195	Ofatumumab N=196
Progression Free Survival^b		
Number of events (%)	35 (17.9)	111 (56.6)
Disease progression	26	93
Death events	9	18
Median (95% CI), months	NE	8.1 (7.2, 8.3)
HR (95% CI)	0.22 (0.15, 0.32)	
Overall Survival^a		
Number of deaths (%)	16 (8.2)	33 (16.8)
HR (95% CI)	0.43 (0.24, 0.79)	
Overall Response Rate ^b	42.6%	4.1%

^a Median OS not evaluable for either arm

^b IRC evaluated. All partial responses achieved; none of the patients achieved a complete response.

CI = confidence interval; HR = hazard ratio; NE = not evaluable

Figure 1: Kaplan-Meier Curve of Progression Free Survival (ITT Population) in Patients with CLL/SLL in RESONATE

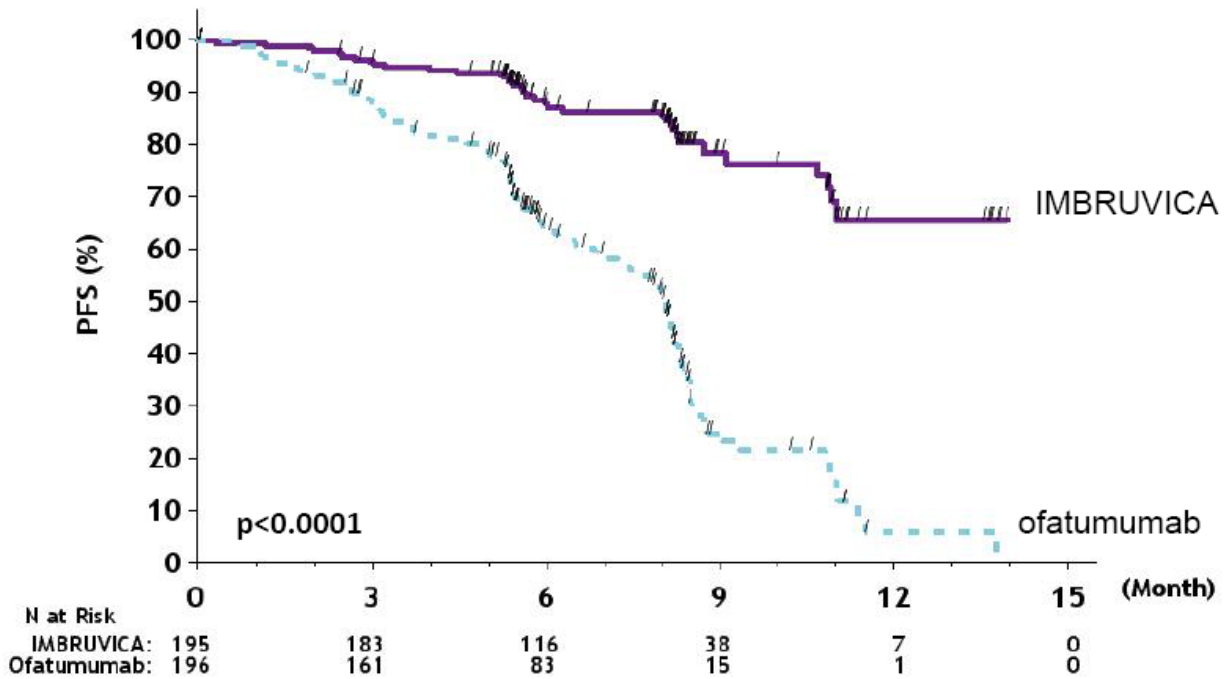
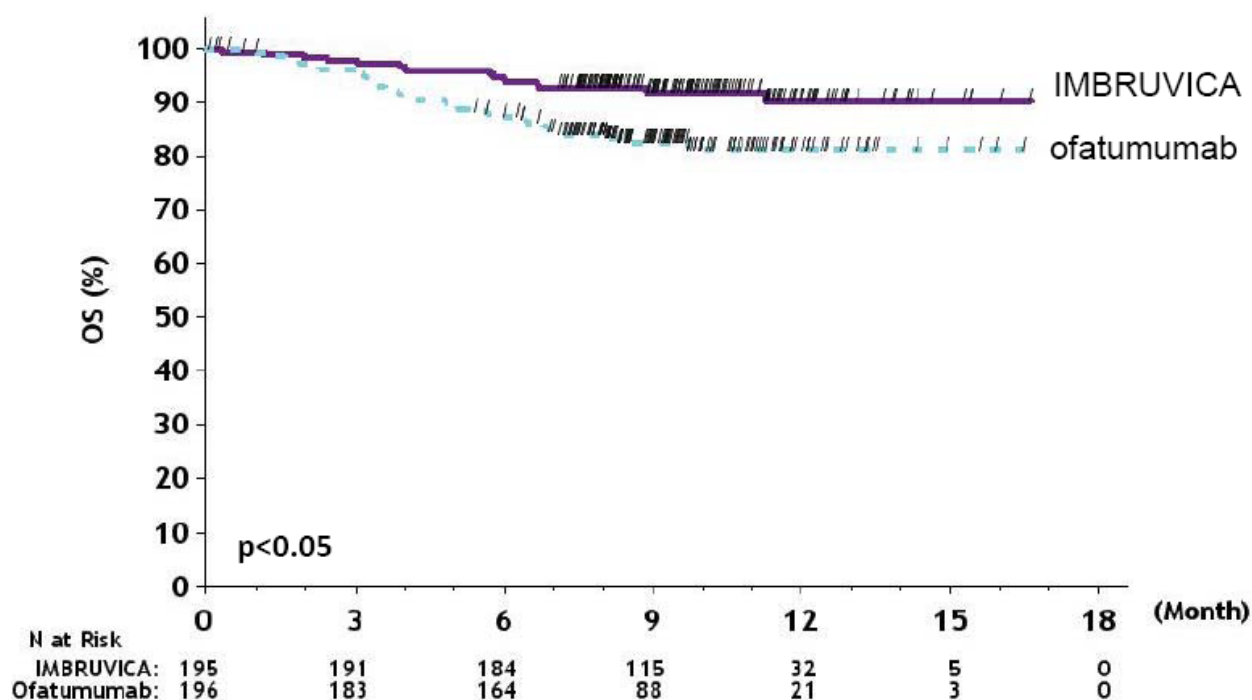


Figure 2: Kaplan-Meier Curve of Overall Survival (ITT Population) in Patients with CLL/SLL in RESONATE



63-Month Follow-Up

With an overall follow-up of 63 months, the median investigator-assessed PFS per IWCLL criteria was 44.1 months [95% CI (38.5, 56.9)] in the IMBRUVICA arm and 8.1 months [95% CI (7.8, 8.3)] in the ofatumumab arm, respectively. Overall response rate as assessed by investigators was 87.2% in the IMBRUVICA arm versus 22.4% in the ofatumumab arm.

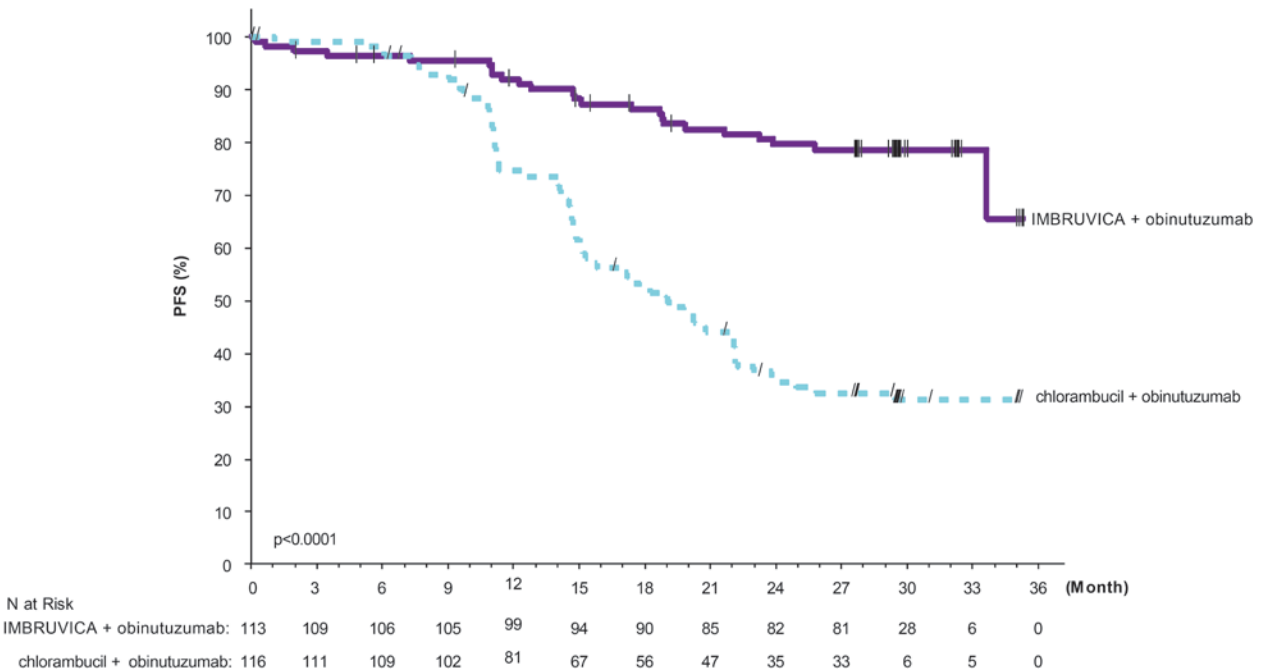
CLL/SLL with 17p deletion (del 17p CLL/SLL) in RESONATE

RESONATE included 127 patients with del 17p CLL/SLL. 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 an IRC. Efficacy results for del 17p CLL/SLL are shown in [Table 19](#).

Table 19: Efficacy Results in Patients with del 17p CLL/SLL in RESONATE

Endpoint	IMBRUVICA N=63	Ofatumumab N=64
Progression Free Survival^a		
Number of events (%)	16 (25.4)	38 (59.4)
Disease progression	12	31
Death events	4	7
Median (95% CI), months	NE	5.8 (5.3, 7.9)

Figure 5: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Patients with CLL/SLL in iLLUMINATE



In the high risk CLL/SLL population (del 17p/TP53 mutation, del 11q, or unmutated IGHV), the PFS HR was 0.15 [95% CI (0.09, 0.27)].

Lymphocytosis

Upon initiation of single-agent IMBRUVICA, an increase in lymphocyte counts (i.e., $\geq 50\%$ increase from baseline and above absolute lymphocyte count of 5,000/mcL) occurred in 66% of patients in the CLL studies. The onset of isolated lymphocytosis occurs during the first month of IMBRUVICA therapy and resolves by a median of 14 weeks (range, 0.1 to 104 weeks). When IMBRUVICA was administered in combination, lymphocytosis was 7% with IMBRUVICA + BR versus 6% with placebo + BR and 7% with IMBRUVICA + obinutuzumab versus 1% with chlorambucil + obinutuzumab.

14.3 Waldenström’s Macroglobulinemia

The safety and efficacy of IMBRUVICA in patients with WM were demonstrated in two single-arm trials and one randomized, controlled trial.

Study 1118 and INNOVATE Monotherapy Arm

The safety and efficacy of IMBRUVICA in WM were evaluated in Study PCYC-1118E (referred to as Study 1118) (NCT01614821), 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 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 23](#).

Table 23: Response Rate and Duration of Response (DOR) Based on IRC Assessment in Patients with WM in Study 1118

	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)	NE (2.8+, 18.8+)

CI = confidence interval; NE = not evaluable

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

The INNOVATE monotherapy arm included 31 patients with previously treated WM who failed prior rituximab-containing therapy and received single-agent IMBRUVICA. The median age was 67 years (range, 47 to 90 years). Eighty-one percent of patients had a baseline ECOG performance status of 0 or 1, and 19% had a baseline ECOG performance status of 2. The median number of prior treatments was 4 (range, 1 to 7 treatments). The response rate observed in the INNOVATE monotherapy arm was 71% (0% CR, 29% VGPR, 42% PR). With a median follow-up time on study of 34 months (range, 8.6+ to 37.7 months), the median duration of response has not been reached.

INNOVATE

The INNOVATE study (A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Ibrutinib or Placebo in Combination with Rituximab in Subjects with Waldenström's Macroglobulinemia) (NCT02165397) was conducted in treatment naïve or previously treated patients with WM. Patients (n = 150) were randomized 1:1 to receive either IMBRUVICA 420 mg daily or placebo in combination with rituximab until disease progression or unacceptable toxicity. Rituximab was administered weekly at a dose of 375 mg/m² for 4 consecutive weeks (weeks 1-4) followed by a second course of weekly rituximab for 4 consecutive weeks (weeks 17-20). The major efficacy outcome measure is progression-free survival (PFS) assessed by an IRC with additional efficacy measure of response rate.

The median age was 69 years (range, 36 to 89 years), 66% were male, and 79% were Caucasian. Ninety-three percent of patients had a baseline ECOG performance status of 0 or 1, and 7% of patients had a baseline ECOG performance status of 2. Forty-five percent of patients were treatment naïve, and 55% of patients were previously treated. Among previously treated patients, the median number of prior treatments was 2 (range, 1 to 6 treatments). At baseline, the median serum IgM value was 3.2 g/dL (range, 0.6 to 8.3 g/dL), and MYD88 L265P mutations were present in 77% of patients, absent in 13% of patients, and 9% of patients were not evaluable for mutation status.

Efficacy results for INNOVATE as assessed by an IRC are shown in [Table 24](#), and the Kaplan-Meier curves for PFS are shown in [Figure 6](#).

Table 24: Efficacy Results in Patients with WM in INNOVATE

Endpoint	IMBRUVICA + R N=75	Placebo + R N=75
Progression Free Survival		
Number of events (%)	14 (19)	42 (56)
Median (95% CI), months	NE	20.3 (13.7, 27.6)
HR (95% CI)	0.20 (0.11, 0.38)	
P-value ^a	<0.0001	
Response Rate (CR+VGPR+PR)^b	72%	32%
95% CI	(0.62, 0.82)	(0.21, 0.43)
Complete Response (CR)	3%	1%
Very Good Partial Response (VGPR)	23%	4%
Partial Response (PR)	47%	27%
Median duration of response, months (range)	NE (1.9+, 36.4+)	21.2 (4.6, 25.8)

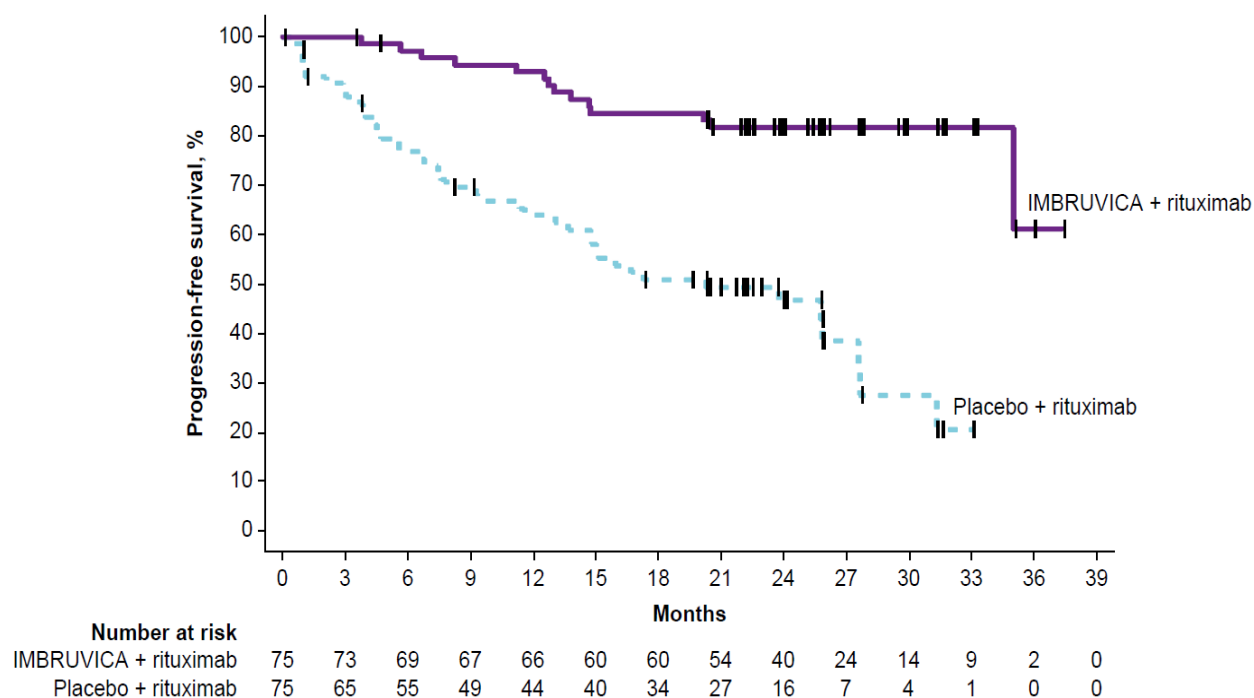
CI = confidence interval; HR = hazard ratio; NE = not evaluable; R = rituximab

^a P-value is from log-rank test stratified by WM IPSS (low, med, high) and number of prior systemic treatment regimens (0, ≥1)

^b P-value associated with response rate was <0.0001.

Median follow-up time on study = 26.5 months

Figure 6: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Patients with WM in INNOVATE



An exploratory analysis demonstrated a sustained hemoglobin improvement (defined as increase of ≥ 2 g/dL over baseline for at least 8 weeks without blood transfusions or growth factor support) in 65% of patients in the IMBRUVICA + R group and 39% of patients in the placebo + R group.

14.4 Marginal Zone Lymphoma

The safety and efficacy of IMBRUVICA in MZL were evaluated in Study PCYC-1121-CA (referred to as Study 1121) (NCT01980628), an open-label, multi-center, single-arm trial of patients who received at least one prior therapy. The efficacy analysis included 63 patients with 3 sub-types of MZL: mucosa-associated lymphoid tissue (MALT; N=32), nodal (N=17), and splenic (N=14). The median age was 66 years (range, 30 to 92 years), 59% were female, and 84% were Caucasian. Ninety two percent of patients had a baseline ECOG performance status of 0 or 1 and 8% had ECOG performance status 2. The median time since diagnosis was 3.8 years, and the median number of prior treatments was 2 (range, 1 to 9 treatments).

IMBRUVICA was administered orally at 560 mg once daily until disease progression or unacceptable toxicity. The responses were assessed by investigators and an IRC using criteria adopted from the International Working Group criteria for malignant lymphoma. Responses per IRC are shown in [Table 25](#).

Table 25: Overall Response Rate (ORR) and Duration of Response (DOR) Based on IRC Assessment in Patients with MZL in Study 1121

	Total (N=63)
Response rate (CR + PR), (%)	46.0%
95% CI (%)	(33.4, 59.1)
Complete Response (CR), (%)	3.2
Partial Response (PR), (%)	42.9
Median duration of response, months (range)	NE (16.7, NE)

CI = confidence interval; NE = not evaluable

Median follow-up time on study = 19.4 months

The median time to response was 4.5 months (range, 2.3 to 16.4 months). Overall response rates were 46.9%, 41.2%, and 50.0% for the 3 MZL sub-types (MALT, nodal, splenic), respectively.

14.5 Chronic Graft versus Host Disease

The safety and efficacy of IMBRUVICA in cGVHD were evaluated in Study PCYC-1129-CA (referred to as Study 1129) (NCT02195869), an open-label, multi-center, single-arm trial of 42 patients with cGVHD after failure of first line corticosteroid therapy and requiring additional therapy. The median age was 56 years (range, 19 to 74 years), 52% were male, and 93% were Caucasian. The most common underlying malignancies leading to transplantation were acute lymphocytic leukemia, acute myeloid leukemia, and CLL. The median time since cGVHD diagnosis was 14 months, the median number of prior cGVHD treatments was 2 (range, 1 to 3 treatments), and 60% of patients had a Karnofsky performance score of ≤ 80 . The majority of patients (88 %) had at least 2 organs involved at baseline, with the most commonly involved organs being mouth (86%), skin (81%), and gastrointestinal tract (33%). The median daily corticosteroid dose (prednisone or prednisone equivalent) at baseline was 0.3 mg/kg/day, and 52% of patients were receiving ongoing immunosuppressants in addition to systemic corticosteroids at baseline. Prophylaxis for infections were managed per institutional guidelines with 79% of patients receiving combinations of sulfonamides and trimethoprim and 64% receiving triazole derivatives.

IMBRUVICA was administered orally at 420 mg once daily. The responses were assessed by investigators using the 2005 National Institute of Health (NIH) Consensus Panel Response Criteria with two modifications to align with the updated 2014 NIH Consensus Panel Response Criteria. Efficacy results are shown in [Table 26](#).

- 280 mg tablets: Purple oblong tablets debossed with “ibr” on one side and “280” on the other side. Carton of one folded blister card containing two 14-count blister strips for a total of 28 tablets: NDC 57962-280-28
- 420 mg tablets: Yellow green to green oblong tablets debossed with “ibr” on one side and “420” on the other side. Carton of one folded blister card containing two 14-count blister strips for a total of 28 tablets: NDC 57962-420-28
- 560 mg tablets: Yellow to orange oblong tablets debossed with “ibr” on one side and “560” on the other side. Carton of one folded blister card containing two 14-count blister strips for a total of 28 tablets: NDC 57962-560-28

Store tablets in original packaging 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).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

- *Hemorrhage:*
Inform patients of the possibility of bleeding, and to report any signs or symptoms (severe headache, 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)*].
- *Cardiac Arrhythmias:*
Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, and chest discomfort [see *Warnings and Precautions (5.4)*].
- *Hypertension:*
Inform patients that high blood pressure has occurred in patients taking IMBRUVICA, which may require treatment with anti-hypertensive therapy [see *Warnings and Precautions (5.5)*].
- *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 (5.6)*].
- *Tumor lysis syndrome:*
Inform patients of the potential risk of tumor lysis syndrome and to report any signs and symptoms associated with this event to their healthcare provider for evaluation [see *Warnings and Precautions (5.7)*].

- *Embryo-fetal toxicity:*
Advise women of the potential hazard to a fetus and to avoid becoming pregnant during treatment and for 1 month after the last dose of IMBRUVICA [*see Warnings and Precautions (5.8)*].
- Inform patients to take IMBRUVICA orally once daily according to their physician's instructions and that the oral dosage (capsules or tablets) should be swallowed whole with a glass of water without opening, breaking or chewing the capsules or cutting, crushing or chewing the tablets 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 doses to make up the missed dose [*see Dosage and Administration (2.6)*].
- 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 [*see Adverse Reactions (6.1)*].

Active ingredient made in China.

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Sunnyvale, CA USA 94085
and

Marketed by:

Janssen Biotech, Inc.
Horsham, PA USA 19044

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

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PATIENT INFORMATION

IMBRUVICA (im-BRU-vih-kuh)
(ibrutinib)
capsules

IMBRUVICA (im-BRU-vih-kuh)
(ibrutinib)
tablets

What is IMBRUVICA?

IMBRUVICA is a prescription medicine used to treat adults with:

- Mantle cell lymphoma (MCL) who have received at least one prior treatment
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL) with 17p deletion
- Waldenström's macroglobulinemia (WM)
- Marginal zone lymphoma (MZL) who require a medicine by mouth or injection (systemic therapy) and have received a certain type of prior treatment
- Chronic graft versus host disease (cGVHD) after failure of 1 or more lines of systemic therapy

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

Before taking 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. If you are able to become pregnant, your healthcare provider will do a pregnancy test before starting treatment with IMBRUVICA.
 - **Females** should not become pregnant during treatment and for 1 month after the last dose of IMBRUVICA.
 - **Males** should avoid getting female partners pregnant during treatment and for 1 month after the last dose of IMBRUVICA.
- are breastfeeding or plan to breastfeed. You and your healthcare provider should decide if you will take IMBRUVICA or breastfeed.

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 and tablets whole with a glass of water.
- Do not open, break, or chew IMBRUVICA capsules.
- Do not cut, crush, or chew IMBRUVICA tablets.
- 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 extra doses of IMBRUVICA to make up for a missed dose.
- If you take too much IMBRUVICA call your healthcare provider or go to the nearest hospital emergency room right away.

What should I avoid while taking IMBRUVICA?

You should not drink grapefruit juice, eat grapefruit, or eat Seville oranges (often used in marmalades) during treatment with 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 (hemorrhage) are common** during treatment with IMBRUVICA, and can also be serious and may lead to death. Your risk of bleeding may increase if you are also taking a blood thinner medicine. 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
 - dizziness
 - weakness
 - confusion
 - change in your speech
 - headache that lasts a long time
- **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 during treatment with 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 (ventricular arrhythmias, atrial fibrillation and atrial flutter).** Serious heart rhythm problems and death 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. If you develop any of these symptoms, your healthcare provider may do a test to check your heart (ECG) and may change your IMBRUVICA dose.
- **High blood pressure (hypertension).** New or worsening high blood pressure has happened in people treated with IMBRUVICA. Your healthcare provider may start you on blood pressure medicine or change current medicines to treat your blood pressure.
- **Second primary cancers.** New cancers have happened during treatment 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.

The most common side effects of IMBRUVICA in adults with B-cell malignancies (MCL, CLL/SLL, WM and MZL) include:

- diarrhea
- muscle and bone pain
- rash
- bruising
- nausea
- tiredness
- fever

The most common side effects of IMBRUVICA in adults with cGVHD include:

- tiredness
- bruising
- diarrhea
- mouth sores (stomatitis)
- muscle spasms
- nausea
- pneumonia

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

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:

IMBRUVICA capsules: croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The 70 mg capsule shell contains gelatin, titanium dioxide, yellow iron oxide, and black ink. The 140 mg capsule shell contains gelatin, titanium dioxide, and black ink.

IMBRUVICA tablets: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium lauryl sulfate. The film coating for each tablet contains ferrousferrous oxide (140 mg, 280 mg, and 420 mg tablets), polyvinyl alcohol, polyethylene glycol, red iron oxide (280 mg and 560 mg tablets), talc, titanium dioxide, and yellow iron oxide (140 mg, 420 mg, and 560 mg tablets).

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For more information, go to www.imbruvica.com or call 1-877-877-3536.

This Patient Information has been approved by the U.S. Food and Drug Administration.

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