

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

IMBRUVICA® (ibrutinib) capsules, for oral use

Initial U.S. Approval: 2013

-----RECENT MAJOR CHANGES-----

| | |
|----------------------------------|--------|
| Indications and Usage (1.2, 1.3) | 5/2016 |
| Dosage and Administration (2.2) | 5/2016 |
| Warnings and Precautions (5) | 3/2016 |

-----INDICATIONS AND USAGE-----

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

- Mantle cell lymphoma (MCL) who have received at least one prior therapy (1.1).

Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.

- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL) (1.2).
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL) with 17p deletion (1.3).
- Waldenström's macroglobulinemia (WM) (1.4).

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

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

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

-----DOSAGE FORMS AND STRENGTHS-----

Capsule: 140 mg (3)

-----CONTRAINDICATIONS-----

None (4)

-----WARNINGS AND PRECAUTIONS-----

- Hemorrhage: Monitor for bleeding and manage (5.1).

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

-----ADVERSE REACTIONS-----

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

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

-----DRUG INTERACTIONS-----

- CYP3A Inhibitors: Avoid co-administration with strong and moderate CYP3A inhibitors. If a moderate CYP3A inhibitor must be used, reduce IMBRUVICA dose (2.4, 7.1).
- CYP3A Inducers: Avoid co-administration with strong CYP3A inducers (7.2).

-----USE IN SPECIFIC POPULATIONS-----

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

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

Revised: 6/2016

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Mantle Cell Lymphoma

IMBRUVICA is indicated for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials [see *Clinical Studies (14.1)*].

1.2 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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

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

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

1.4 Waldenström's Macroglobulinemia

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

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Guidelines

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

2.2 Dosage

Mantle Cell Lymphoma

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

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

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

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

2.3 Dose Modifications for Adverse Reactions

Interrupt IMBRUVICA therapy for any Grade 3 or greater non-hematological toxicities, Grade 3 or greater neutropenia with infection or fever, or Grade 4 hematological toxicities. Once the symptoms of the toxicity have resolved to Grade 1 or baseline (recovery), IMBRUVICA therapy may be reinitiated at the starting dose. If the toxicity reoccurs, reduce dose by one capsule (140 mg per day). A second reduction of dose by 140 mg may be considered as needed. If these toxicities persist or recur following two dose reductions, discontinue IMBRUVICA.

Recommended dose modifications are described below:

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

2.4 Dose Modifications for Use with CYP3A Inhibitors

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

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

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

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

2.5 Dose Modifications for Use in Hepatic Impairment

For patients with mild liver impairment (Child-Pugh class A), the recommended dose is 140 mg daily (one capsule). Avoid the use of IMBRUVICA in patients with moderate or severe hepatic impairment (Child-Pugh classes B and C) [see *Use in Specific Populations (8.6)* and *Clinical Pharmacology (12.3)*].

2.6 Missed Dose

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

3 DOSAGE FORMS AND STRENGTHS

140 mg capsules

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Hemorrhage

Fatal bleeding events have occurred in patients treated with IMBRUVICA. Grade 3 or higher bleeding events (intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with IMBRUVICA.

The mechanism for the bleeding events is not well understood.

IMBRUVICA may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding.

Consider the benefit-risk of withholding IMBRUVICA for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding [see *Clinical Studies (14)*].

5.2 Infections

Fatal and non-fatal infections have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 14% to 29% of patients [see *Adverse Reactions (6.1), (6.2)*]. Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with IMBRUVICA. Evaluate patients for fever and infections and treat appropriately.

5.3 Cytopenias

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

Monitor complete blood counts monthly.

5.4 Atrial Fibrillation

Atrial fibrillation and atrial flutter (range, 6 to 9%) have occurred in patients treated with IMBRUVICA, particularly in patients with cardiac risk factors, hypertension, acute infections,

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

5.5 Hypertension

Hypertension (range, 6 to 17%) has occurred in patients treated with IMBRUVICA with a median time to onset of 4.6 months (range, 0.03 to 22 months). Monitor patients for new onset hypertension or hypertension that is not adequately controlled after starting IMBRUVICA. Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

5.6 Second Primary Malignancies

Other malignancies (range, 5 to 16%) including non-skin carcinomas (range, 1 to 4%) have occurred in patients treated with IMBRUVICA. The most frequent second primary malignancy was non-melanoma skin cancer (range, 4 to 13%).

5.7 Tumor Lysis Syndrome

Tumor lysis syndrome has been infrequently reported with IMBRUVICA therapy. Assess the baseline risk (e.g., high tumor burden) and take appropriate precautions. Monitor patients closely and treat as appropriate.

5.8 Embryo-Fetal Toxicity

Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis caused embryofetal toxicity including malformations at exposures that were 2-20 times higher than those reported in patients with MCL, CLL/SLL or WM. Advise women to avoid becoming pregnant while taking IMBRUVICA and for 1 month after cessation of therapy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus [see *Use in Specific Populations (8.1)*].

6 ADVERSE REACTIONS

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

- Hemorrhage [see *Warnings and Precautions (5.1)*]
- Infections [see *Warnings and Precautions (5.2)*]
- Cytopenias [see *Warnings and Precautions (5.3)*]
- Atrial Fibrillation [see *Warnings and Precautions (5.4)*]
- Hypertension [see *Warnings and Precautions (5.5)*]

- 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 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 4 (%) |
|---|-----------------------------------|----------------|------------------|
| 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 | 7 |
| | 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 |
| | Arthralgia | 11 | 0 |
| Respiratory, thoracic and mediastinal disorders | Dyspnea | 27 | 4 |
| | 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 |

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/Small Lymphocytic Lymphoma

The data described below reflect exposure in one single-arm, open-label clinical trial and three randomized controlled clinical trials in patients with CLL/SLL (n=1278 total and n=668 patients exposed to IMBRUVICA). Study 1 included 51 patients with previously treated CLL/SLL, Study 2 included 391 randomized patients with previously treated CLL or SLL who received single agent IMBRUVICA or ofatumumab, Study 3 included 269 randomized patients 65 years or older with treatment naïve-CLL or SLL who received single agent IMBRUVICA or chlorambucil and Study 4 included 578 randomized patients with previously treated CLL or SLL who received IMBRUVICA in combination with bendamustine and rituximab or placebo in combination with bendamustine and rituximab.

The most commonly occurring adverse reactions in Studies 1, 2, 3 and 4 in patients with CLL/SLL receiving IMBRUVICA ($\geq 20\%$) were neutropenia, thrombocytopenia, anemia, diarrhea, musculoskeletal pain, nausea, rash, bruising, fatigue, pyrexia and hemorrhage. Four to 10 percent of patients receiving IMBRUVICA in Studies 1, 2, 3 and 4 discontinued treatment due to adverse reactions. These included pneumonia, hemorrhage, atrial fibrillation, rash and neutropenia (1% each). Adverse reactions leading to dose reduction occurred in approximately 6% of patients.

Study 1

Adverse reactions and laboratory abnormalities from the CLL/SLL trial (N=51) using single agent IMBRUVICA 420 mg daily in patients with previously treated CLL/SLL occurring at a rate of $\geq 10\%$ with a median duration of treatment of 15.6 months are presented in [Tables 3](#) and [4](#).

Table 3: Non-Hematologic Adverse Reactions in $\geq 10\%$ of Patients with CLL/SLL (N=51) in Study 1

| Body System | Adverse Reaction | All Grades (%) | Grade 3 or 4 (%) |
|---|-----------------------------------|-----------------------|-------------------------|
| Gastrointestinal disorders | Diarrhea | 59 | 4 |
| | Constipation | 22 | 2 |
| | Nausea | 20 | 2 |
| | Stomatitis | 20 | 0 |
| | Vomiting | 18 | 2 |
| | Abdominal pain | 14 | 0 |
| | Dyspepsia | 12 | 0 |
| Infections and infestations | Upper respiratory tract infection | 47 | 2 |
| | Sinusitis | 22 | 6 |
| | Skin infection | 16 | 6 |
| | Pneumonia | 12 | 10 |
| | Urinary tract infection | 12 | 2 |
| General disorders and administration site conditions | Fatigue | 33 | 6 |
| | Pyrexia | 24 | 2 |
| | Peripheral edema | 22 | 0 |
| | Asthenia | 14 | 6 |
| | Chills | 12 | 0 |
| Skin and subcutaneous tissue disorders | Bruising | 51 | 2 |
| | Rash | 25 | 0 |
| | Petechiae | 16 | 0 |
| Respiratory, thoracic and mediastinal disorders | Cough | 22 | 0 |
| | Oropharyngeal pain | 14 | 0 |
| | Dyspnea | 12 | 0 |
| Musculoskeletal and connective tissue disorders | Musculoskeletal pain | 25 | 6 |
| | Arthralgia | 24 | 0 |
| | Muscle spasms | 18 | 2 |
| Nervous system disorders | Dizziness | 20 | 0 |
| | Headache | 18 | 2 |
| Metabolism and nutrition disorders | Decreased appetite | 16 | 2 |
| Neoplasms benign, malignant, unspecified | Second malignancies* | 12* | 0 |
| Vascular disorders | Hypertension | 16 | 8 |

*One patient death due to histiocytic sarcoma.

Table 4: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with CLL/SLL (N=51) in Study 1

| | Percent of Patients (N=51) | |
|-----------------------|----------------------------|------------------|
| | All Grades (%) | Grade 3 or 4 (%) |
| Platelets Decreased | 69 | 12 |
| Neutrophils Decreased | 53 | 26 |
| Hemoglobin Decreased | 43 | 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 in patients with previously treated CLL/SLL.

Table 5: Adverse Reactions Reported in $\geq 10\%$ of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients in Study 2

| Body System Adverse Reaction | IMBRUVICA (N=195) | | Ofatumumab (N=191) | |
|---|----------------------|---------------------|-----------------------|---------------------|
| | All Grades (%) | Grade 3 or 4 (%) | All Grades (%) | Grade 3 or 4 (%) |
| Gastrointestinal disorders | | | | |
| 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 |
| General disorders and administration site conditions | | | | |
| Pyrexia | 24 | 2 | 15 | 1 |
| Infections and infestations | | | | |
| 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 |
| Skin and subcutaneous tissue disorders | | | | |
| Rash* | 24 | 3 | 13 | 0 |
| Petechiae | 14 | 0 | 1 | 0 |
| Bruising* | 12 | 0 | 1 | 0 |

| Body System Adverse Reaction | IMBRUVICA (N=195) | | Ofatumumab (N=191) | |
|--|----------------------|---------------------|-----------------------|---------------------|
| | All Grades (%) | Grade 3 or 4 (%) | All Grades (%) | Grade 3 or 4 (%) |
| Musculoskeletal and connective tissue disorders | | | | |
| Musculoskeletal Pain* | 28 | 2 | 18 | 1 |
| Arthralgia | 17 | 1 | 7 | 0 |
| Nervous system disorders | | | | |
| Headache | 14 | 1 | 6 | 0 |
| Dizziness | 11 | 0 | 5 | 0 |
| Injury, poisoning and procedural complications | | | | |
| Contusion | 11 | 0 | 3 | 0 |
| Eye disorders | | | | |
| 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.

Study 3

Adverse reactions described below in [Table 7](#) reflect exposure to IMBRUVICA with a median duration of 17.4 months. The median exposure to chlorambucil was 7.1 months in Study 3.

Table 7: Adverse Reactions Reported in $\geq 10\%$ of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients in Study 3

| Body System Adverse Reaction | IMBRUVICA (N=135) | | Chlorambucil (N=132) | |
|---|----------------------|---------------------|-------------------------|---------------------|
| | All Grades (%) | Grade 3 or 4 (%) | All Grades (%) | Grade 3 or 4 (%) |
| Gastrointestinal disorders | | | | |
| Diarrhea | 42 | 4 | 17 | 0 |
| Stomatitis* | 14 | 1 | 4 | 1 |
| Musculoskeletal and connective tissue disorders | | | | |
| Musculoskeletal pain* | 36 | 4 | 20 | 0 |
| Arthralgia | 16 | 1 | 7 | 1 |
| Muscle spasms | 11 | 0 | 5 | 0 |
| Eye Disorders | | | | |
| Dry eye | 17 | 0 | 5 | 0 |
| Lacrimation increased | 13 | 0 | 6 | 0 |
| Vision blurred | 13 | 0 | 8 | 0 |
| Visual acuity reduced | 11 | 0 | 2 | 0 |
| Skin and subcutaneous tissue disorders | | | | |
| Rash* | 21 | 4 | 12 | 2 |
| Bruising* | 19 | 0 | 7 | 0 |
| Infections and infestations | | | | |
| Skin infection* | 15 | 2 | 3 | 1 |
| Pneumonia* | 14 | 8 | 7 | 4 |
| Urinary tract infections | 10 | 1 | 8 | 1 |
| Respiratory, thoracic and mediastinal disorders | | | | |
| Cough | 22 | 0 | 15 | 0 |
| General disorders and administration site conditions | | | | |
| Peripheral edema | 19 | 1 | 9 | 0 |
| Pyrexia | 17 | 0 | 14 | 2 |
| Vascular Disorders | | | | |
| Hypertension* | 14 | 4 | 1 | 0 |
| Nervous System Disorders | | | | |
| Headache | 12 | 1 | 10 | 2 |

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

Study 4

Adverse reactions described below in Table 8 reflect exposure to IMBRUVICA + BR with a median duration of 14.7 months and exposure to placebo + BR with a median of 12.8 months in Study 4 in patients with previously treated CLL/SLL.

Table 8: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients in Study 4

| Body System Adverse Reaction | Ibrutinib + BR (N=287) | | Placebo + BR (N=287) | |
|---|---------------------------|---------------------|-------------------------|---------------------|
| | All Grades (%) | Grade 3 or 4 (%) | All Grades (%) | Grade 3 or 4 (%) |
| Blood and lymphatic system disorders | | | | |
| Neutropenia* | 66 | 61 | 60 | 55 |
| Thrombocytopenia* | 34 | 16 | 26 | 16 |
| Skin and subcutaneous tissue disorders | | | | |
| Rash * | 32 | 4 | 25 | 1 |
| Bruising * | 20 | <1 | 8 | <1 |
| Gastrointestinal disorders | | | | |
| Diarrhea | 36 | 2 | 23 | 1 |
| Abdominal Pain | 12 | 1 | 8 | <1 |
| Musculoskeletal and connective tissue disorders | | | | |
| Musculoskeletal pain * | 29 | 2 | 20 | 0 |
| Muscle spasms | 12 | <1 | 5 | 0 |
| General disorders and administration site conditions | | | | |
| Pyrexia | 25 | 4 | 22 | 2 |
| Vascular Disorders | | | | |
| Hemorrhage* | 19 | 2 | 9 | 1 |
| Hypertension * | 11 | 5 | 5 | 2 |
| Infections and infestations | | | | |
| Bronchitis | 13 | 2 | 10 | 3 |
| Skin infection* | 10 | 3 | 6 | 2 |
| Metabolism and nutrition disorders | | | | |
| Hyperuricemia | 10 | 2 | 6 | 0 |

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

* Includes multiple ADR terms

<1 used for frequency above 0 and below 0.5%

Atrial fibrillation of any grade occurred in 7% of patients treated with IMBRUVICA + BR and 2% of patients treated with placebo + BR. The frequency of Grade 3 and 4 atrial fibrillation was 3% in patients treated with IMBRUVICA + BR and 1% in patients treated with placebo +BR.

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 9 and 10 reflect exposure to IMBRUVICA with a median duration of 11.7 months in the WM trial.

Table 9: Non-Hematologic Adverse Reactions in $\geq 10\%$ of Patients with Waldenström’s Macroglobulinemia (N=63)

| Body System | Adverse Reaction | 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 preferred terms are sorted in descending frequency order.

* Includes multiple ADR terms.

Table 10: 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.

Additional Important Adverse Reactions

Diarrhea

Diarrhea of any grade occurred at a rate of 43% (range, 36% to 63%) of patients treated with IMBRUVICA. Grade 2 diarrhea occurred in 9% (range, 3% to 15%) and Grade 3 in 3% (range, 0 to 5%) of patients treated with IMBRUVICA. The median time to first onset of any grade diarrhea was 12 days (range, 0 to 627), of Grade 2 was 37 days (range, 1 to 667) and of Grade 3 was 71 days (range, 3 to 627). Of the patients who reported diarrhea, 83% had complete resolution, 1% had partial improvement and 16% had no reported improvement at time of analysis. The median time from onset to resolution or improvement of any grade diarrhea was 5 days (range, 1 to 418), and was similar for Grades 2 and 3. Less than 1% of patients discontinued IMBRUVICA due to diarrhea.

Visual Disturbance

Blurred vision and decreased visual acuity of any grade occurred in 10% of patients treated with IMBRUVICA (9% Grade 1, 2% Grade 2). The median time to first onset was 88 days (range, 1 to 414 days). Of the patients with visual disturbance, 64% had complete resolution and 36% had no reported improvement at time of analysis. The median time from onset to resolution or improvement was 29 days (range, 1 to 281 days).

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 (includes multiple terms)

Respiratory disorders: interstitial lung disease (includes multiple terms)

Metabolic and nutrition disorders: tumor lysis syndrome [see *Warnings & Precautions (5.7)*]

Skin and subcutaneous tissue disorders: anaphylactic shock, angioedema, urticaria

7 DRUG INTERACTIONS

7.1 CYP3A Inhibitors

Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A (CYP3A). 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 ± 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

Risk Summary

IMBRUVICA, a kinase inhibitor, can cause fetal harm based on findings from animal studies. 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 malformations [*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.

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.

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 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 infant, 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

Verify the pregnancy status of 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 839 patients in clinical studies of IMBRUVICA, 62% were ≥ 65 years of age, while 21% were ≥ 75 years of age. No overall differences in effectiveness were observed between younger and older patients. Grade 3 or higher pneumonia occurred more frequently among older patients treated with IMBRUVICA [see *Clinical Studies (14.2)*].

8.6 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 cancer patients with mild to severe hepatic impairment by Child-Pugh criteria.

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 class B and C) [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.

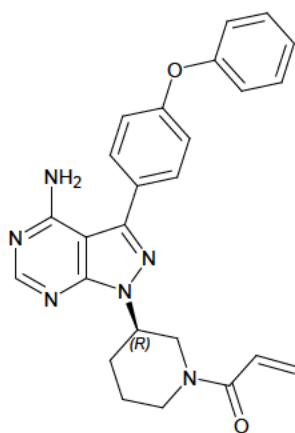
10 OVERDOSAGE

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

In healthy subjects, at a single dose 3 times the maximum recommended dose (1680 mg), ibrutinib did not prolong the QT interval to any clinically relevant extent.

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 ± 705 ng·h/mL and in patients at 420 mg is 680 ± 517 ng·h/mL. Absolute bioavailability in fasted condition ($n = 8$) was 2.9% (90% CI = 2.1 – 3.9) and doubled when combined with a meal. 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 (V_d) 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 [^{14}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

In older patients (67 to 81 years), there is a 14% higher ibrutinib exposure predicted. Dose adjustment by age is not warranted.

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 (CrCL) > 25 mL/min had no influence on the exposure to IMBRUVICA. There are no data in patients with severe renal impairment (CrCL < 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_{max} 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 (8.6)*].

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_{max} 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_{max} 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-gp (p-glycoprotein) or BCRP (breast cancer resistance protein) transporters but is an in vitro inhibitor of P-gp and BCRP. Systemic ibrutinib is unlikely to be an inhibitor of P-gp at clinical doses ($[I]_1/K_i < 0.1$) but may inhibit BCRP. Ibrutinib may have an effect on P-gp or BCRP substrates in the GI tract due to higher local concentrations after an oral dose. Co-administration of oral narrow therapeutic index P-gp or BCRP substrates (e.g., digoxin, methotrexate) 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.

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 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 11.

Table 11: Overall Response Rate (ORR) and Duration of Response (DOR) Based on Investigator Assessment in Patients with MCL

| | 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, 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 / Small Lymphocytic Lymphoma

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

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 ≥ 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, multi-center, 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 ≥ 5 cm. Thirty-two percent of patients had 17p deletion.

Efficacy results for Study 2 are shown in [Table 12](#) and the Kaplan-Meier curves for PFS, assessed by independent review committee (IRC) according to IWCLL criteria, and OS are shown in [Figures 1](#) and [2](#), respectively.

Table 12: Efficacy Results in Study 2

| 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 | NR | 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 reached for either arm

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

CI = confidence interval; HR = hazard ratio; NR = not reached

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

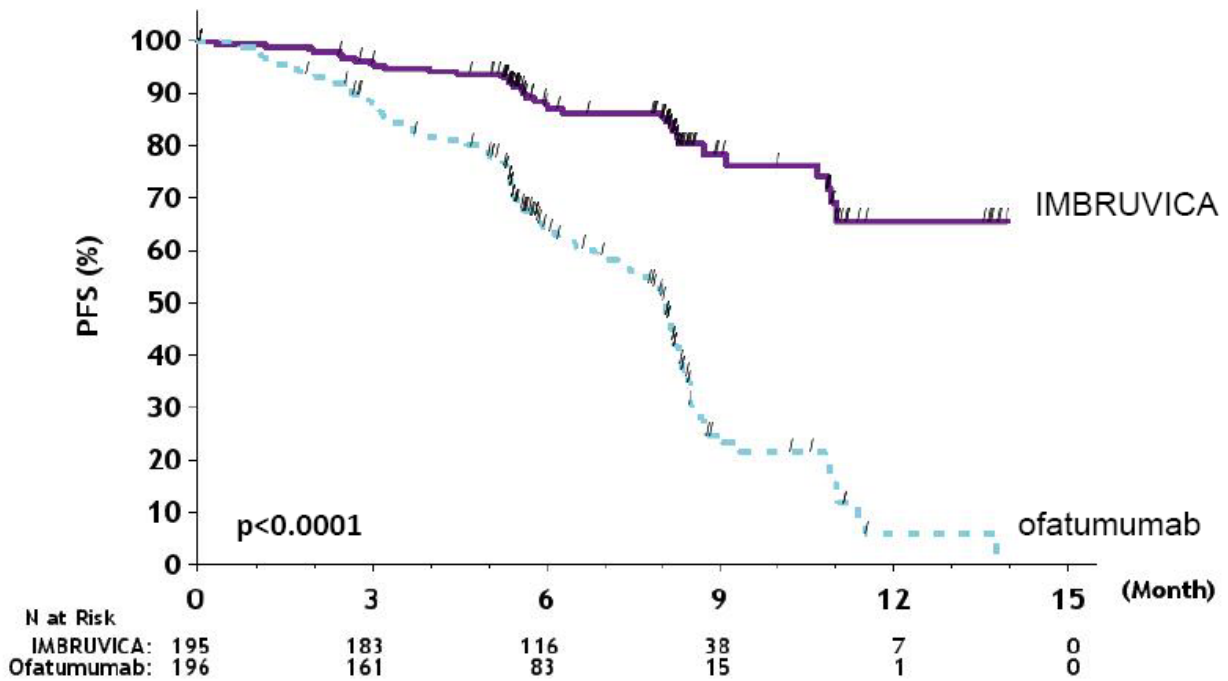
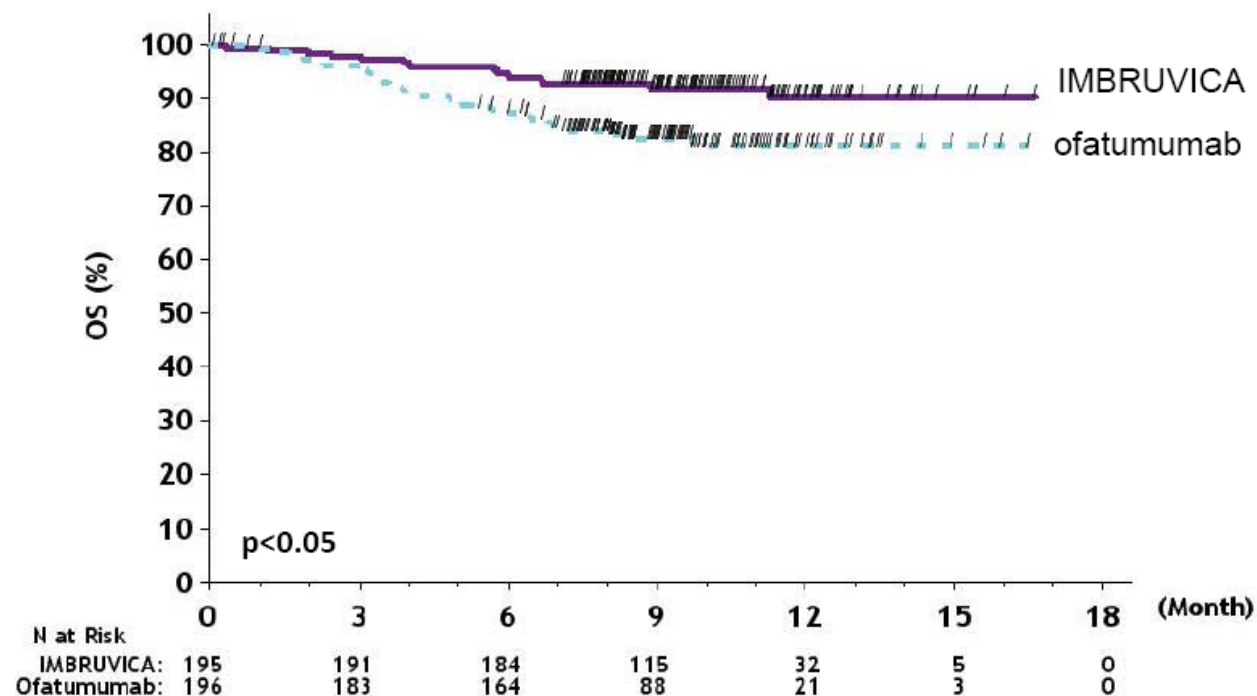


Figure 2: Kaplan-Meier Curve of Overall Survival (ITT Population) in Study 2



CLL/SLL with 17p deletion (del 17p CLL/SLL) in Study 2

Study 2 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 IRC. Efficacy results for del 17p CLL/SLL are shown in Table 13.

Table 13: Efficacy Results in Patients with del 17p CLL/SLL in Study 2

| 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 | NR | 5.8 (5.3, 7.9) |
| HR (95% CI) | 0.25 (0.14, 0.45) | |
| Overall Response Rate ^a | 47.6% | 4.7% |

^a IRC evaluated. All partial responses achieved; none of the patients achieved a complete response. CI = confidence interval; HR = hazard ratio; NR = not reached

Study 3

A randomized, multi-center, open-label study of IMBRUVICA versus chlorambucil was conducted in patients with treatment naïve CLL or SLL who were 65 years of age or older. Patients (n = 269) were randomized 1:1 to receive either IMBRUVICA 420 mg daily until disease progression or unacceptable toxicity, or chlorambucil at a starting dose of 0.5 mg/kg on Days 1 and 15 of each 28-day cycle for a maximum of 12 cycles, with an allowance for inpatient dose increases up to 0.8 mg/kg based on tolerability.

The median age was 73 years (range, 65 to 90 years), 63% were male, and 91% were Caucasian. Ninety one percent of patients had a baseline ECOG performance status of 0 or 1 and 9% had an ECOG performance status of 2. The trial enrolled 249 patients with CLL and 20 patients with SLL. At baseline, 20% of patients had 11q deletion. The most common reasons for initiating CLL therapy include: progressive marrow failure demonstrated by anemia and/or thrombocytopenia (38%), progressive or symptomatic lymphadenopathy (37%), progressive or symptomatic splenomegaly (30%), fatigue (27%) and night sweats (25%).

With a median follow-up of 28.1 months, there were 32 observed death events [11 (8.1%) and 21 (15.8%) in IMBRUVICA and chlorambucil treatment arms, respectively]. With 41% of patients switching from chlorambucil to IMBRUVICA, the overall survival analysis in the ITT patient population resulted in a statistically significant HR of 0.44 [95% CI (0.21, 0.92)] and 2-year survival rate estimates of 94.7% [95% CI (89.1, 97.4)] and 84.3% [95% CI (76.7, 89.6)] in the IMBRUVICA and chlorambucil arms, respectively.

Efficacy results for Study 3 are shown in Table 14 and the Kaplan-Meier curve for PFS, assessed by independent review committee (IRC) according to IWCLL criteria is shown in [Figure 3](#).

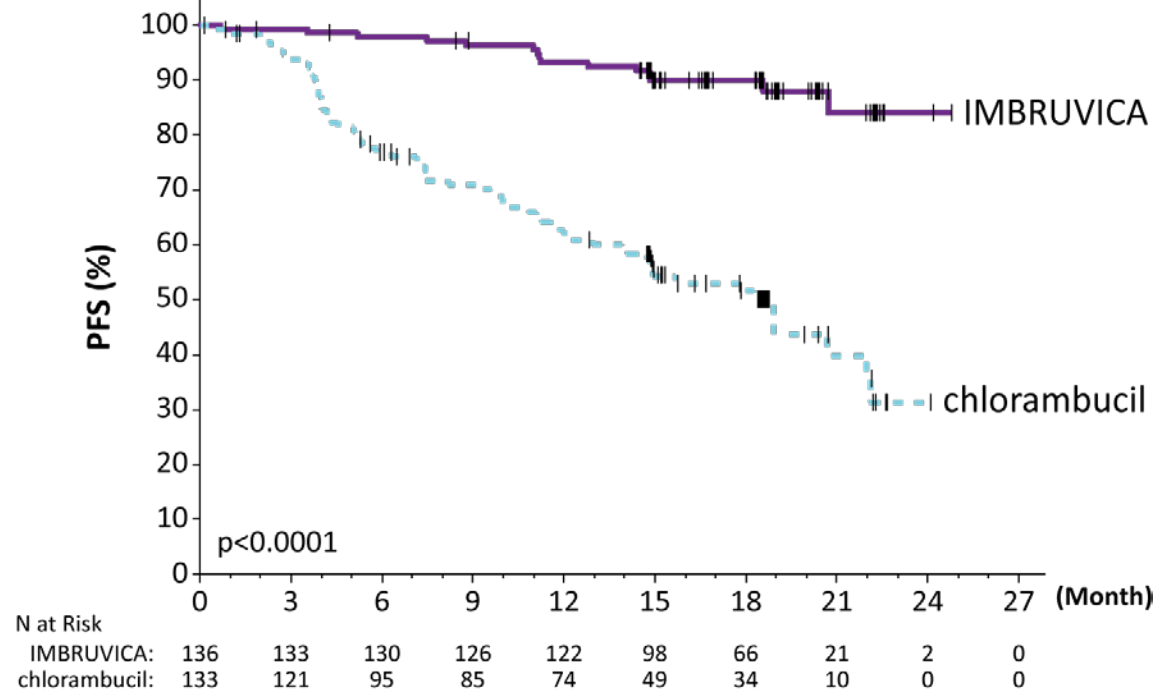
Table 14: Efficacy Results in Study 3

| Endpoint | IMBRUVICA N=136 | Chlorambucil N=133 |
|--|--------------------|-----------------------|
| Progression Free Survival^a | | |
| Number of events (%) | 15 (11.0) | 64 (48.1) |
| Disease progression | 12 | 57 |
| Death events | 3 | 7 |
| Median (95% CI), months | NR | 18.9 (14.1, 22.0) |
| HR ^b (95% CI) | 0.16 (0.09, 0.28) | |
| Overall Response Rate^a (CR + PR) | 82.4% | 35.3% |
| P-value | <0.0001 | |

^a IRC evaluated; Five subjects (3.7%) in the IMBRUVICA arm and two subjects (1.5%) in the Chlorambucil arm achieved complete response

^b HR = hazard ratio; NR = not reached

Figure 3: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Study 3



Study 4

A randomized, multicenter, double-blinded Phase 3 study of IMBRUVICA in combination with bendamustine and rituximab (BR) versus placebo + BR was conducted in patients with previously treated CLL or SLL. Patients (n = 578) were randomized 1:1 to receive either IMBRUVICA 420 mg daily or placebo in combination with BR until disease progression, or unacceptable toxicity. All patients received BR for a maximum of six 28-day cycles.

Bendamustine was dosed at 70 mg/m² infused IV over 30 minutes on Cycle 1, Days 2 and 3, and on Cycles 2-6, Days 1 and 2 for up to 6 cycles. Rituximab was administered at a dose of 375 mg/m² in the first cycle, Day 1, and 500 mg/m² Cycles 2 through 6, Day 1.

The median age was 64 years (range, 31 to 86 years), 66% were male, and 91% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 5.9 years and the median number of prior treatments was 2 (range, 1 to 11 treatments). At baseline, 56% of patients had at least one tumor \geq 5 cm and 26% presented with del11q.

Efficacy results for Study 4 are shown in [Table 15](#) and the Kaplan-Meier curves for PFS are shown in [Figure 4](#).

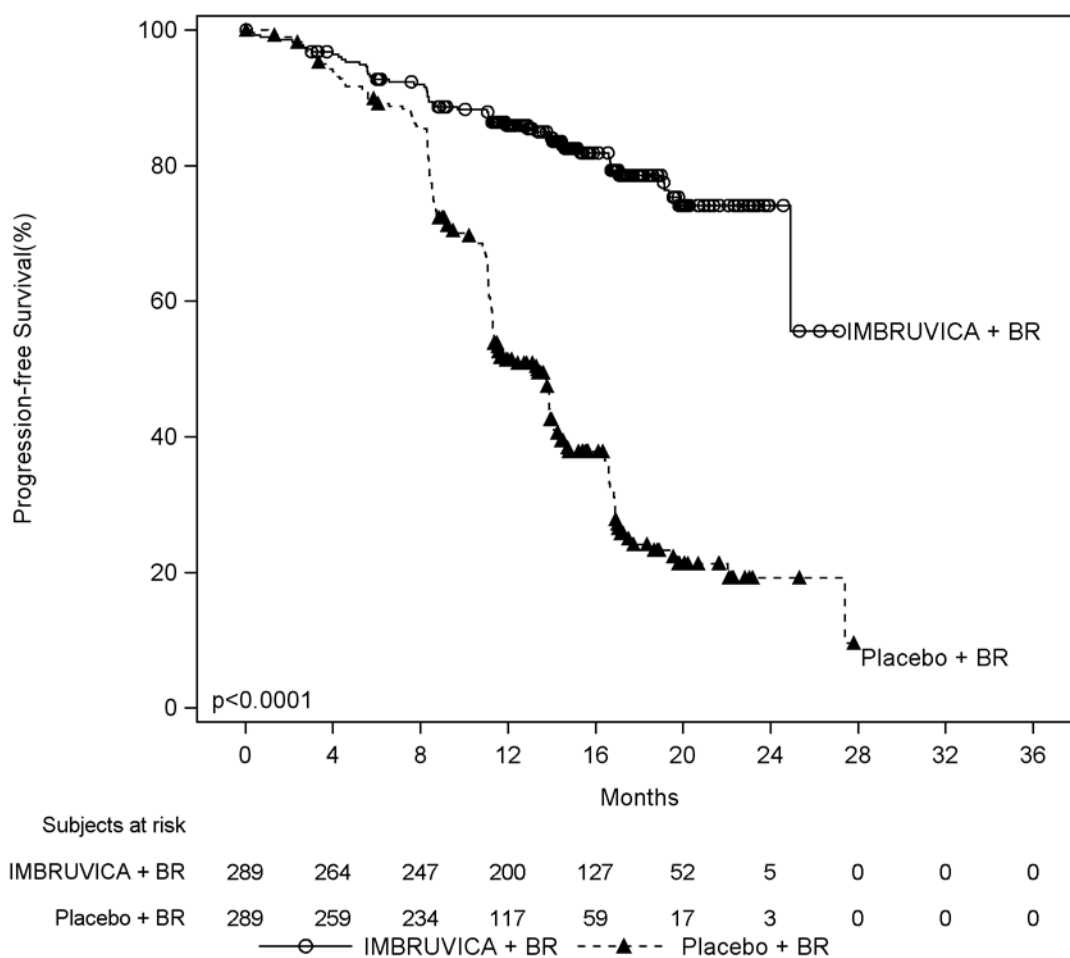
Table 15: Efficacy Results in Study 4

| Endpoint | IMBRUVICA + BR N=289 | Placebo + BR N=289 |
|--|-------------------------|-----------------------|
| Progression Free Survival^a | | |
| Number of events (%) | 56 (19.4) | 183 (63.3) |
| Median (95% CI), months | Not reached | 13.3 (11.3, 13.9) |
| HR (95% CI) | 0.20 (0.15, 0.28) | |
| Overall Response Rate ^a | 82.7% | 67.8% |

^a IRC evaluated, Twenty four subjects (8.3%) in the IMBRUVICA + BR arm and six subjects (2.1%) in the placebo + BR arm achieved complete response

BR = bendamustine and rituximab; CI = confidence interval; HR = hazard ratio

Figure 4: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Study 4



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 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 with chemoimmunotherapy, lymphocytosis was 7% with IMBRUVICA + BR versus 6% with placebo + BR.

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 16.

Table 16: Overall Response Rate (ORR) and Duration of Response (DOR) 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

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)*].
- *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)*].
- *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 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 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 (2.6)*].
- 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.

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/s/

BARRY W MILLER
06/28/2016