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

----------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).

This indication is based on overall response rate. An improvement in survival or disease-related symptoms has not been established (14.1).

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

560 mg taken orally once daily (four 140 mg capsules once daily) (2.2).

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

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

Capsule: 140 mg (3)

----------CONTRAINDICATIONS----------

None

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

- Hemorrhage: Monitor for bleeding (5.1).
- Infections: Monitor patients for fever and infections and evaluate promptly (5.2).
- Myelosuppression: Check complete blood counts monthly (5.3).
- Renal Toxicity: Monitor renal function and maintain hydration (5.4).
- Second Primary Malignancies: Other malignancies have occurred in patients, including skin cancers, and other carcinomas (5.5).
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise women of the potential risk to a fetus and to avoid pregnancy while taking the drug (5.6).

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

The most common adverse reactions (≥20%) in patients with MCL 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 (6).

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

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

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

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

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

Hepatic Impairment: Avoid use of IMBRUVICA in patients with baseline hepatic impairment (8.7).

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

Revised: 11/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

IMBRUVICA is indicated for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. This indication is based on overall response rate. An improvement in survival or disease-related symptoms has not been established *[see Clinical Studies (14.1)]*.

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 for Mantle Cell Lymphoma

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

2.3 Dose Modifications for Adverse Reactions

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

Recommended dose modifications for these toxicities are described below:

Toxicity Occurrence	**MCL Dose Modification After Recovery Starting Dose = 560 mg**
First	Restart at 560 mg daily
Second	Restart at 420 mg daily
Third	Restart at 280 mg daily
Fourth	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, grapefruit products 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 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

Five percent of patients with MCL had Grade 3 or higher bleeding events (subdural hematoma, gastrointestinal bleeding, and hematuria). Overall, bleeding events including bruising of any grade occurred in 48% of patients with MCL treated with 560 mg daily.

The mechanism for the bleeding events is not well understood.

Consider the benefit-risk of ibrutinib in patients requiring antiplatelet or anticoagulant therapies.

Consider the benefit-risk of withholding ibrutinib 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 (14.1)]*.

5.2 Infections

Fatal and non-fatal infections have occurred with IMBRUVICA therapy. At least 25% of patients with MCL had infections Grade 3 or greater NCI Common Terminology Criteria for Adverse Events (CTCAE) *[See Adverse Reactions (6)]*. Monitor patients for fever and infections and evaluate promptly.

5.3 Myelosuppression

Treatment-emergent Grade 3 or 4 cytopenias were reported in 41% of patients. These included neutropenia (29%), thrombocytopenia (17%) and anemia (9%). Monitor complete blood counts monthly.

5.4 Renal Toxicity

Fatal and serious cases of renal failure have occurred with IMBRUVICA therapy. Treatment-emergent increases in creatinine levels up to 1.5 times the upper limit of normal occurred in 67% of patients and from 1.5 to 3 times the upper limit of normal in 9% of patients. Periodically monitor creatinine levels. Maintain hydration.

5.5 Second Primary Malignancies

Other malignancies (5%) have occurred in patients with MCL who have been treated with IMBRUVICA, including skin cancers (4%), and other carcinomas (1%).

5.6 Embryo-Fetal Toxicity

Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Ibrutinib caused malformations in rats at exposures 14 times those reported in patients with MCL receiving the ibrutinib dose of 560 mg per day. Reduced fetal weights were observed at lower exposures. Advise women to avoid becoming pregnant while taking IMBRUVICA. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations (8.1)]*.

6 ADVERSE REACTIONS

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

- Hemorrhage *[see Warnings and Precautions (5.1)]*
- Infections *[see Warnings and Precautions (5.2)]*
- Myelosuppression *[see Warnings and Precautions (5.3)]*
- Renal Toxicity *[see Warnings and Precautions (5.4)]*
- Second Primary Malignancies *[see Warnings and Precautions (5.5)]*

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.

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 (≥ 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 (≥ 5%) were pneumonia, abdominal pain, atrial fibrillation, diarrhea, fatigue, and skin infections.

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

Table 1: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with Mantle Cell Lymphoma (N=111)

System Organ Class	Preferred Term	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 administrative 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 nutritional disorders	Decreased appetite	21	2
	Dehydration	12	4
Nervous system disorders	Dizziness	14	0
	Headache	13	0

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