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
IMBRUVICA® (ibrutinib) tablets, for oral use
IMBRUVICA® (ibrutinib) oral suspension
Initial U.S. Approval: 2013

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

Indications and Usage, cGVHD (1.6)	8/2022
Dosage and Administration (2.1, 2.3, 2.4)	8/2022
Dosage and Administration (2.2)	5/2022
Warnings and Precautions,	
Cardiac Arrhythmias, Cardiac Failure, and Sudden Death (5.3)	5/2022
Hypertension (5.4)	5/2022

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

IMBRUVICA is a kinase inhibitor indicated for the treatment of:

- Adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy (1.1).

  This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).
- Adult patients with chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL) (1.2).
- Adult patients with chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL) with 17p deletion (1.3).
- Adult patients with Waldenström's macroglobulinemia (WM) (1.4).
- Adult patients with marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy (1.5).

  This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).
- Adult and pediatric patients age 1 year and older with chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy (1.6).

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

- MCL and MZL: 560 mg taken orally once daily (2.1).
- CLL/SLL and WM: 420 mg taken orally once daily (2.1).
- cGVHD:
  - Patients 12 years and older: 420 mg taken orally once daily (2.1).
  - Patients 1 to less than 12 years of age: 240 mg/m^2 taken orally once daily (up to a dose of 420 mg) (2.1).

Tablets or capsules 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. See full prescribing information for oral suspension administration instructions (2.1).

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

Capsules: 70 mg and 140 mg (3)
Tablets: 140 mg, 280 mg, 420 mg, and 560 mg (3)
Oral suspension: 70 mg/mL (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).
- Cardiac Arrhythmias, Cardiac Failure, and Sudden Death: Monitor for symptoms of arrhythmias and cardiac failure and manage (5.3).
- Hypertension: Monitor blood pressure and treat (5.4).
- Cytopenias: Check complete blood counts monthly (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 females of reproductive potential of the potential risk to a fetus and to use effective contraception (5.8, 8.1, 8.3).

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

- The most common (≥30%) adverse reactions in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) are thrombocytopenia, diarrhea, fatigue, musculoskeletal pain, neutropenia, rash, anemia, and bruising (6).
- The most common (≥20%) adverse reactions in adult or pediatric patients with cGVHD are fatigue, anemia, bruising, diarrhea, thrombocytopenia, musculoskeletal pain, pyrexia, muscle spasms, stomatitis, hemorrhage, nausea, abdominal pain, pneumonia, and headache (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: Modify IMBRUVICA dose as described (2.3, 7.1).
- CYP3A Inducers: Avoid coadministration with strong CYP3A inducers (7.2).

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

- Lactation: Advise not to breastfeed. (8.2)
- Hepatic Impairment: Avoid use of IMBRUVICA in patients with severe hepatic impairment. In patients with mild or moderate impairment, reduce IMBRUVICA dose (2.4, 8.6).

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

Revised: 8/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Mantle Cell Lymphoma

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

This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s) *[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.

This indication is approved under accelerated approval 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(s).

1.6 Chronic Graft versus Host Disease

IMBRUVICA is indicated for the treatment of adult and pediatric patients age 1 year and older with chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Mantle Cell Lymphoma and Marginal Zone Lymphoma

The recommended dosage 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 dosage of IMBRUVICA for CLL/SLL and WM is 420 mg orally once daily until disease progression or unacceptable toxicity.

For CLL/SLL, IMBRUVICA can be administered as a single agent, in combination with rituximab or obinutuzumab, or in combination with bendamustine and rituximab (BR).

For WM, IMBRUVICA can be administered as a single agent or in combination with rituximab.

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 dosage of IMBRUVICA for patients age 12 years and older with cGVHD is 420 mg orally once daily, and for patients 1 to less than 12 years of age with cGVHD is 240 mg/m^2 orally once daily (up to a dose of 420 mg), 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.

Table 1: Recommended dosage based on body surface area (BSA) for patients 1 to less than 12 years of age using either IMBRUVICA capsules/tablets or oral suspension

	Recommended dose to achieve 240 mg/m^2	
BSA* (m^2) Range	**Dose (mg) of IMBRUVICA Capsules/Tablets to Administer**	**Volume (mL) of IMBRUVICA Oral Suspension (70 mg/mL) to Administer**
> 0.3 to 0.4	-	1.2 mL
> 0.4 to 0.5	-	1.5 mL
> 0.5 to 0.6	-	1.9 mL
> 0.6 to 0.7	-	2.2 mL
> 0.7 to 0.8	210 mg	2.6 mL
> 0.8 to 0.9	210 mg	2.9 mL
> 0.9 to 1.0	210 mg	3.3 mL
> 1.0 to 1.1	280 mg	3.6 mL
> 1.1 to 1.2	280 mg	4 mL
> 1.2 to 1.3	280 mg	4.3 mL
> 1.3 to 1.4	350 mg	4.6 mL
> 1.4 to 1.5	350 mg	5 mL
> 1.5 to 1.6	350 mg	5.3 mL

	Recommended dose to achieve 240 mg/m^2	
BSA* (m^2) Range	**Dose (mg) of IMBRUVICA Capsules/Tablets to Administer**	**Volume (mL) of IMBRUVICA Oral Suspension (70 mg/mL) to Administer**
> 1.6	420 mg	6 mL

*BSA = body surface area.

Administration

Administer IMBRUVICA at approximately the same time each day.

Swallow tablets or capsules whole with a glass of water. Do not open, break, or chew the capsules. Do not cut, crush, or chew the tablets.

Follow Instructions for Use for further administration details of IMBRUVICA oral suspension.

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. Do not take extra doses of IMBRUVICA to make up for the missed dose.

2.2 Dosage Modifications for Adverse Reactions

For adverse reactions listed in Table 2, interrupt IMBRUVICA therapy. Once the adverse reaction has improved to Grade 1 or baseline (recovery), follow the recommended dosage modifications (see Table 2).

Table 2: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction[a,b]	**Occurrence**	**Dose Modification for MCL and MZL After Recovery Starting Dose = 560 mg**	**Dose Modification for CLL/SLL, WM, and Patients 12 Years or older with cGVHD After Recovery Starting Dose = 420 mg**	**Dose Modification for Patients 1 Year to less than 12 Years with cGVHD After Recovery Starting Dose = 240 mg/m^2**
Grade 2 cardiac failure	First	Restart at 420 mg daily[c]	Restart at 280 mg daily[c]	Restart at 160 mg/m^2 daily[c]
	Second	Restart at 280 mg daily[c]	Restart at 140 mg daily[c]	Restart at 80 mg/m^2 daily[c]
	Third	Discontinue IMBRUVICA	Discontinue IMBRUVICA	Discontinue IMBRUVICA
Grade 3 cardiac arrhythmias	First	Restart at 420 mg daily[c]	Restart at 280 mg daily[c]	Restart at 160 mg/m^2 daily[c]

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