An Important Message for Patients and Healthcare Professionals Who Depend on IMBRUVICA® (ibrutinib)

IMBRUVICA® (ibrutinib) is a meaningful and important treatment option for patients with chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), mantle cell lymphoma (MCL), Waldenström's macroglobulinemia (WM), marginal zone lymphoma (MZL), and chronic graft versus host disease (cGVHD). *Please see the complete indications and important safety information for IMBRUVICA in this document and* full Prescribing Information.

IMBRUVICA is brought to patients jointly by Pharmacyclics and Janssen.

You may have seen recent media coverage about the new single-tablet formulation of IMBRUVICA. Nothing is more important to us than the health of patients who depend on our medicines, and we want you to know the following:

Dosing

- In the robust clinical studies that led to U.S. FDA approval, IMBRUVICA demonstrated significant improvement in survival rates when dosed at 420 mg for CLL and in response rates when dosed at 560 mg for MCL and MZL. These are the recommended doses for these diseases in the FDA-approved label. Consistent with the IMBRUVICA label, healthcare professionals may decide to reduce their patient's dosage because the patient has had an adverse reaction or because they're taking certain other medicines at the same time.
- As part of our comprehensive clinical program, we conducted a dose-finding study that started at lower doses and determined that the optimal doses to achieve the best outcomes were those now approved in the label.
- **While physicians are free to exercise their independent medical judgement on what is right for their patients, there is extremely limited data investigating the use of lower doses of IMBRUVICA. We do not know if lower doses will result in the same clinical outcomes as the approved doses.**
- To our knowledge, there have been no peer-reviewed publications of prospective studies exploring clinical outcomes associated with lower doses of IMBRUVICA.
- We welcome and appreciate the work of researchers and clinicians who are contributing to the expanding knowledge about this important treatment. As we learn more about IMBRUVICA through ongoing clinical trials and real-world use, we will apply these learnings to improve the patient experience and patient outcomes.

New Single-Tablet Formulation

- Since we introduced IMBRUVICA, patients have had to take 3 or 4 pills every day to get the recommended dose – a total of between 1,095 and 1,460 pills each year.
- Starting in 2015, we began development of a new single-tablet formulation of IMBRUVICA to give patients a simple one pill, once-a-day dosing regimen. Independent research has demonstrated that one-pill, once-

daily regimens can lead to improved adherence (compliance with doctor's orders on how to take a medicine), and better adherence can lead to improved outcomes.

- The new single-tablet formulation was approved by the U.S. FDA in February 2018 and is now available.
- We recognize that healthcare professionals may need to reduce the dose for patients who are experiencing adverse reactions or are taking certain other medicines at the same time. The YOU&i™ Dose Exchange Program is available to facilitate this dose reduction if a healthcare professional decides to adjust their patient's dose before they have finished their current pack of IMBRUVICA. As a safety-based returns program, patients will receive their new dose of IMBRUVICA at no additional cost through rapid shipment to ensure continuity of care.

Pricing

- The new single tablet is priced at one price no matter the dose, similar to many other oral oncology medicines with varying dose strengths. The price is based on the most widely prescribed and lower of the two FDA-approved dosages, which is 420 mg per day. While a patient's out-of-pocket cost for IMBRUVICA is ultimately determined by their insurance plan, the vast majority of patients (i.e., patients taking 420 mg and 560 mg doses of IMBRUVICA) will likely see no increase in out-of-pocket costs when transitioning to the single-tablet formulation. In fact, current patients on the 560 mg dose will likely see a decrease in their out-of-pocket costs. Out-of-pocket expenses may increase for patients who are taking a lower dose of IMBRUVICA (140 mg or 280 mg).
- We offer comprehensive access and support services to qualifying patients in the U.S. through the YOU&i™ Support Program. Patients can contact the YOU&i™ Support Program at www.imbruvica.com or by calling us at 1-877-877-3536. We also offer a YOU&i™ Instant Savings Program to help commercially insured, eligible patients with their out-of-pocket expenses for IMBRUVICA.
- We are not permitted by federal law to directly help patients who are on federally funded health coverage, such as Medicare, with copay assistance for their out-of-pocket costs.
- For patients with federally funded Medicare, Medicaid, or commercial insurance, independent charitable foundation support may be available to patients who qualify.
- We are listening to healthcare professionals and patients and, as always, take their feedback seriously and will continue to apply what we learn to improve our approach.

The extensive clinical trials that went into the approval of IMBRUVICA, and our more than 30 clinical trials that are still underway, reflect our commitment to changing the future for patients facing tough-to-treat blood cancers.

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Additional Information about IMBRUVICA®

INDICATIONS

IMBRUVICA® is indicated to treat adults with[i]

- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL) with 17p deletion
- Waldenström's macroglobulinemia (WM)
- Mantle cell lymphoma (MCL) patients 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.
- Marginal zone lymphoma (MZL) patients 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. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
- Chronic Graft-Versus-Host Disease (cGVHD) patients who failed one or more lines of systemic therapy

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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.

Infections: Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 14% to 29% of patients. 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.

Cytopenias: Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 13 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 13%) based on laboratory measurements occurred in patients with B-cell malignancies treated with single agent IMBRUVICA®.
Monitor complete blood counts monthly.

Cardiac Arrhythmias: Fatal and serious cardiac arrhythmias have occurred with IMBRUVICA® therapy. Grade 3 or greater ventricular tachyarrhythmias occurred in 0 to 1% of patients, and Grade 3 or greater atrial fibrillation and atrial flutter occurred in 0 to 6% of patients. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias.

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**.**

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.

Second Primary Malignancies: Other malignancies (range, 3 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, 2 to 13%).

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.

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA® can cause fetal harm when administered to a pregnant woman. 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. Advise men to avoid fathering a child during the same time period.

ADVERSE REACTIONS

B-cell malignancies: The most common adverse reactions (≥20%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were thrombocytopenia (62%)*, neutropenia (61%)*, diarrhea (43%), anemia (41%)*, musculoskeletal pain (30%), bruising (30%), rash (30%), fatigue (29%), nausea (29%), hemorrhage (22%), and pyrexia (21%).

The most common Grade 3 or 4 adverse reactions (≥5%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia (39%)*, thrombocytopenia (16%)*, and pneumonia (10%).

Approximately 6% (CLL/SLL), 14% (MCL), 11% (WM) and 10% (MZL) of patients had a dose reduction due to adverse reactions. Approximately 4%-10% (CLL/SLL), 9% (MCL), and 9 % (WM [6%] and MZL [13%]) of patients discontinued due to adverse reactions.

cGVHD: The most common adverse reactions (≥20%) in patients with cGVHD were fatigue (57%), bruising (40%), diarrhea (36%), thrombocytopenia (33%)*, stomatitis (29%), muscle spasms (29%), nausea (26%), hemorrhage (26%), anemia (24%)*, and pneumonia (21%).

The most common Grade 3 or 4 adverse reactions (≥5%) reported in patients with cGVHD were fatigue (12%), diarrhea (10%), neutropenia (10%)*, pneumonia (10%), sepsis (10%), hypokalemia (7%), headache (5%), musculoskeletal pain (5%), and pyrexia (5%).

Twenty-four percent of patients receiving IMBRUVICA® in the cGVHD trial discontinued treatment due to adverse reactions. Adverse reactions leading to dose reduction occurred in 26% of patients.
*Treatment-emergent decreases (all grades) were based on laboratory measurements and adverse reactions.

DRUG INTERACTIONS

CYP3A Inhibitors: Dose adjustments may be recommended.

CYP3A Inducers: Avoid coadministration with strong CYP3A inducers.

SPECIFIC POPULATIONS

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

Please see Full Prescribing Information: https://www.imbruvica.com/prescribing-information.

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[i] Janssen Biotech, Inc., Pharmacyclics LLC. IMBRUVICA U.S. Prescribing Information. February 2018.