



## **News Release**

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## **Update on IMBRUVICA® (ibrutinib) U.S. Accelerated Approvals for Mantle Cell Lymphoma and Marginal Zone Lymphoma Indications**

**HORSHAM, Pa., April 6, 2023** – The Janssen Pharmaceutical Companies of Johnson & Johnson, in collaboration with its alliance partner, Pharmacyclics, an AbbVie Company, announced today the intent to voluntarily withdraw the U.S. indications for IMBRUVICA® (ibrutinib) for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy, and for the treatment of patients with marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy. This decision was made in consultation with the U.S. Food and Drug Administration (FDA), consistent with FDA procedural guidance on accelerated approvals. This decision does not affect any other approved indications for IMBRUVICA® in the U.S. Janssen will be communicating directly with healthcare professionals to help support patients currently receiving treatment with IMBRUVICA® in the U.S. for MCL or MZL.

The FDA previously granted approval for IMBRUVICA® in MCL and MZL based on overall response rates in two Phase 2 clinical studies under the accelerated approval pathway.

Continued approval was contingent upon demonstration of clinical benefit in the confirmatory Phase 3 SHINE study ([NCT01776840](#)) in previously untreated patients with MCL, and the confirmatory Phase 3 SELENE study ([NCT01974440](#)) in patients with relapsed or refractory (R/R) follicular lymphoma (FL) or MZL. The companies fully enrolled the Phase 3 studies within approximately one year of the accelerated approvals. After discussing the study results with the companies, the FDA advised that the primary outcomes from the Phase 3 confirmatory studies for the indications were considered insufficient to support conversion to full approval.

“We fully support the FDA accelerated approval pathway, which patients rely on for timely access to promising treatments that may improve or extend their lives. While withdrawing these indications was a difficult decision, we remain confident in the benefit/risk profile of IMBRUVICA in its approved indications and are committed to its continued development,” said Craig Tendler, M.D., Vice President, Late Development and Global Medical Affairs, Janssen Research & Development, LLC. “IMBRUVICA has transformed how patients with B-cell malignancies are treated and is the most comprehensively studied and prescribed therapy in its class.”

The Phase 3 SHINE study met its primary endpoint and demonstrated a significant progression-free survival advantage in patients with previously untreated MCL but did not show an overall survival advantage. The addition of IMBRUVICA® to chemoimmunotherapy was associated with increased adverse reactions compared to the placebo-controlled arm. The SHINE study results were presented during the 2022 American Society of Clinical Oncology annual meeting and were published in [The New England Journal of Medicine](#). The Phase 3 SELENE study did not meet its primary endpoint of progression-free survival in patients with R/R FL or MZL. The SELENE study results will be presented at a future scientific forum.

### **About IMBRUVICA® in MCL and MZL Outside the United States**

IMBRUVICA® has been used to treat more than 270,000 patients worldwide. This Bruton’s tyrosine kinase (BTK) inhibitor is approved for R/R MCL in more than 100 countries outside the U.S. based on positive clinical data from the Phase 2 PCYC-1104 study ([NCT01236391](#)) and the randomized Phase 3 RAY study ([NCT01646021](#)). In addition, IMBRUVICA® is approved for R/R MZL in more than 30 countries outside the U.S. based on the Phase 2

PCYC-1121 study ([NCT01980628](#)). IMBRUVICA® remains an important therapy for patients and healthcare professionals around the world.

### **About MCL and MZL**

MCL and MZL, both subtypes of non-Hodgkin's Lymphoma (NHL), are rare and serious blood cancers.<sup>1,2</sup> MCL accounts for approximately five percent and MZL accounts for approximately seven percent of all cases of NHL in adults and approximately 80,000 people will be diagnosed with NHL in 2023.<sup>1,2,3</sup> MCL occurs in the white blood cells and is marked by small-to medium-size cancer cells in the lymph nodes, spleen, bone marrow, blood, or gastrointestinal system.<sup>4</sup> MZL occurs in white blood cells (lymphocytes) at the edges of lymph nodes and various tissues, including the stomach, salivary glands, thyroid gland, eyes, lungs and spleen.<sup>5,6</sup> MCL and MZL are difficult to treat, and therefore treatment options are limited.<sup>7,8</sup>

### **About IMBRUVICA®**

IMBRUVICA® (ibrutinib) is a once-daily oral medication that is jointly developed and commercialized by Janssen Biotech, Inc. and Pharmacyclics LLC, an AbbVie company. IMBRUVICA® blocks the BTK protein, which is needed by normal and abnormal B cells, including specific cancer cells, to multiply and spread. By blocking BTK, IMBRUVICA® may help move abnormal B cells out of their nourishing environments and inhibits their proliferation.<sup>9,10,11</sup>

IMBRUVICA® is approved in more than 100 countries and has been used to treat more than 270,000 patients worldwide. There are more than 50 company-sponsored clinical trials, including 18 Phase 3 studies, and more than 11 years evaluating the efficacy and safety of IMBRUVICA®.

IMBRUVICA® was first approved by the U.S. FDA in November 2013, and today is indicated for adult patients in four disease areas, including three hematologic cancers. These include indications to treat adults with chronic lymphocytic leukemia (CLL)/ small lymphocytic lymphoma (SLL) with or without 17p deletion (del17p); adults with Waldenström's macroglobulinemia (WM); and adult and pediatric patients aged one year and older with previously treated chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy.<sup>12</sup>

For more information, visit [www.IMBRUVICA.com](http://www.IMBRUVICA.com).

## **IMPORTANT SAFETY INFORMATION**

### **WARNINGS AND PRECAUTIONS**

**Hemorrhage:** Fatal bleeding events have occurred in patients who received IMBRUVICA®. Major hemorrhage (≥ Grade 3, serious, or any central nervous system events; e.g., intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post procedural hemorrhage) occurred in 4.2% of patients, with fatalities occurring in 0.4% of 2,838 patients who received IMBRUVICA® in 27 clinical trials. Bleeding events of any grade including bruising and petechiae occurred in 39%, and excluding bruising and petechiae occurred in 23% of patients who received IMBRUVICA®, respectively.

The mechanism for the bleeding events is not well understood.

Use of either anticoagulant or antiplatelet agents concomitantly with IMBRUVICA® increases the risk of major hemorrhage. Across clinical trials, 3.1% of 2,838 patients who received IMBRUVICA® without antiplatelet or anticoagulant therapy experienced major hemorrhage. The addition of antiplatelet therapy with or without anticoagulant therapy increased this percentage to 4.4%, and the addition of anticoagulant therapy with or without antiplatelet therapy increased this percentage to 6.1%. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with IMBRUVICA®. Monitor for signs and symptoms of bleeding.

Consider the benefit-risk of withholding IMBRUVICA® for at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

**Infections:** Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 21% of 1,476 patients who received IMBRUVICA® in clinical trials. 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.

**Cardiac Arrhythmias, Cardiac Failure, and Sudden Death:** Fatal and serious cardiac arrhythmias and cardiac failure have occurred with IMBRUVICA®. Deaths due to cardiac causes or sudden deaths occurred in 1% of 4,896 patients who received IMBRUVICA® in clinical trials, including in patients who received IMBRUVICA® in unapproved monotherapy or combination regimens. These adverse reactions occurred in patients with and without preexisting hypertension or cardiac comorbidities. Patients with cardiac comorbidities may be at greater risk of these events.

Grade 3 or greater ventricular tachyarrhythmias were reported in 0.2%, Grade 3 or greater atrial fibrillation and atrial flutter were reported in 3.7%, and Grade 3 or greater cardiac failure was reported in 1.3% of 4,896 patients who received IMBRUVICA® in clinical trials, including in patients who received IMBRUVICA® in unapproved monotherapy or combination regimens. These events have occurred particularly in patients with cardiac risk factors including hypertension and diabetes mellitus, a previous history of cardiac arrhythmias, and in patients with acute infections.

Evaluate cardiac history and function at baseline, and monitor patients for cardiac arrhythmias and cardiac function. Obtain further evaluation (e.g., ECG, echocardiogram) as indicated for patients who develop symptoms of arrhythmia (e.g., palpitations, lightheadedness, syncope, chest pain), new onset dyspnea, or other cardiovascular concerns. Manage cardiac arrhythmias and cardiac failure appropriately, follow dose modification guidelines, and consider the risks and benefits of continued IMBRUVICA® treatment.

**Hypertension:** Hypertension occurred in 19% of 1,476 patients who received IMBRUVICA® in clinical trials. Grade 3 or greater hypertension occurred in 8% of patients. Based on data from 1,124 of these patients, the median time to onset was 5.9 months (range, 0.03 to 24 months). Monitor blood pressure in patients treated with IMBRUVICA®, initiate or adjust anti-hypertensive medication throughout treatment with IMBRUVICA® as appropriate, and follow dosage modification guidelines for Grade 3 or higher hypertension.

**Cytopenias:** In 645 patients with B-cell malignancies who received IMBRUVICA® as a single agent, Grade 3 or 4 neutropenia occurred in 23% of patients, Grade 3 or 4

thrombocytopenia in 8% and Grade 3 or 4 anemia in 2.8%, based on laboratory measurements. Monitor complete blood counts monthly.

**Second Primary Malignancies:** Other malignancies (10%), including non-skin carcinomas (3.9%), occurred among the 1,476 patients who received IMBRUVICA® in clinical trials. The most frequent second primary malignancy was non-melanoma skin cancer (6%).

**Tumor Lysis Syndrome:** Tumor lysis syndrome has been infrequently reported with IMBRUVICA®. 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 pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with IMBRUVICA® and for 1 month after the last dose. Advise males with female partners of reproductive potential to use effective contraception during the same time period.

## **ADVERSE REACTIONS**

**B-cell malignancies:** The most common adverse reactions ( $\geq 30\%$ ) in adult patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were thrombocytopenia (54.5%)\*, diarrhea (43.8%), fatigue (39.1%), musculoskeletal pain (38.8%), neutropenia (38.6%)\*, rash (35.8%), anemia (35.0%)\*, and bruising (32.0%).

The most common Grade  $\geq 3$  adverse reactions ( $\geq 5\%$ ) in adult patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia (20.7%)\*, thrombocytopenia (13.6%)\*, pneumonia (8.2%), and hypertension (8.0%).

Approximately 9% (CLL/SLL), 14% (MCL), 14% (WM) and 10% (MZL) of adult patients had a dose reduction due to adverse reactions. Approximately 4-10% (CLL/SLL), 9% (MCL), and 7% (WM [5%] and MZL [13%]) of patients discontinued due to adverse reactions.

**cGVHD:** The most common adverse reactions ( $\geq 20\%$ ) in adult or pediatric patients with cGVHD were fatigue (57%), anemia (49%)\*, bruising (40%), diarrhea (36%),

thrombocytopenia (33%)\*, musculoskeletal pain (30%), pyrexia (30%), muscle spasms (29%), stomatitis (29%), hemorrhage (26%), nausea (26%), abdominal pain (23%), pneumonia (23%), and headache (21%).

The most common Grade 3 or higher adverse reactions ( $\geq 5\%$ ) reported in adult or pediatric patients with cGVHD were pneumonia (14%), anemia (13%)\*, fatigue (12%), pyrexia (11%), diarrhea (10%), neutropenia (10%)\*, sepsis (10%), osteonecrosis (9%), stomatitis (9%), hypokalemia (7%), headache (5%), and musculoskeletal pain (5%).

Discontinuation of IMBRUVICA<sup>®</sup> treatment due to an adverse reaction occurred in 24% of adult patients and 23% of pediatric patients. Adverse reactions leading to dose reduction occurred in 26% of adult patients and 19% of pediatric patients.

\*Treatment-emergent decreases (all grades) were based on laboratory measurements.

## **DRUG INTERACTIONS**

**CYP3A Inhibitors:** Co-administration of IMBRUVICA<sup>®</sup> with strong or moderate CYP3A inhibitors may increase ibrutinib plasma concentrations. Increased ibrutinib concentrations may increase the risk of drug-related toxicity. Dose modifications of IMBRUVICA<sup>®</sup> are recommended when used concomitantly with 7-oxa-azoles, voriconazole, and moderate CYP3A inhibitors. Avoid concomitant use of other strong CYP3A inhibitors. Interrupt IMBRUVICA<sup>®</sup> if strong inhibitors are used short-term (e.g., for  $\leq 7$  days). Avoid grapefruit and Seville oranges during IMBRUVICA<sup>®</sup> treatment, as these contain strong or moderate inhibitors of CYP3A. See dose modification guidelines in USPI sections 2.3 and 7.1.

**CYP3A Inducers:** Avoid coadministration with strong CYP3A inducers.

## **SPECIFIC POPULATIONS**

### **Pediatric Use:**

The safety and effectiveness of IMBRUVICA<sup>®</sup> have been established for treatment of cGVHD after failure of one or more lines of systemic therapy in pediatric patients 1 year of age and older. The safety and effectiveness of IMBRUVICA<sup>®</sup> have not been established for this

indication in pediatric patients less than 1 year of age.

The safety and effectiveness of IMBRUVICA® in pediatric patients have not been established in MCL, CLL/SLL, CLL/SLL with 17p deletion, WM, or MZL.

The safety and effectiveness of IMBRUVICA® in combination with chemoimmunotherapy were assessed but have not been established based on an open-label, randomized study (NCT02703272) in 35 patients, which included 26 pediatric patients age 5 to less than 17 years, with previously treated mature B-cell non-Hodgkin lymphoma. In the randomized population, major hemorrhage and discontinuation of chemoimmunotherapy due to adverse reactions occurred more frequently in the ibrutinib plus chemoimmunotherapy arm compared to the chemoimmunotherapy alone arm.

### **Hepatic Impairment:**

Adult Patients with B-cell Malignancies: Hepatic Impairment (based on Child-Pugh criteria): Avoid use of IMBRUVICA® in patients with severe hepatic impairment. In patients with mild or moderate impairment, reduce recommended IMBRUVICA® dose and monitor more frequently for adverse reactions of IMBRUVICA®.

Patients with cGVHD: Avoid use of IMBRUVICA® in patients with total bilirubin level > 3x upper limit of normal (ULN) (unless of non-hepatic origin or due to Gilbert's syndrome). Reduce recommended dose when administering IMBRUVICA® to patients with total bilirubin level >1.5 to 3x ULN (unless of non-hepatic origin or due to Gilbert's syndrome).

Please click [here](#) to see the full Prescribing Information

### **About the Janssen Pharmaceutical Companies of Johnson & Johnson**

At Janssen, we're creating a future where disease is a thing of the past. We're the Pharmaceutical Companies of Johnson & Johnson, working tirelessly to make that future a reality for patients everywhere by fighting sickness with science, improving access with ingenuity and healing hopelessness with heart. We focus on areas of medicine where we can make the biggest difference: Cardiovascular, Metabolism & Retina; Immunology; Infectious Diseases & Vaccines; Neuroscience; Oncology; and Pulmonary Hypertension.

Learn more at [www.janssen.com](http://www.janssen.com). Follow us at [@JanssenUS](https://twitter.com/JanssenUS) and [@JanssenGlobal](https://twitter.com/JanssenGlobal). Janssen Biotech, Inc. and Janssen Research & Development, LLC are part of the Janssen Pharmaceutical Companies of Johnson & Johnson.

### **Cautions Concerning Forward-Looking Statements**

*This press release contains "forward-looking statements" as defined in the Private Securities Litigation Reform Act of 1995 regarding IMBRUVICA® (ibrutinib). The reader is cautioned not to rely on these forward-looking statements. These statements are based on current expectations of future events. If underlying assumptions prove inaccurate or known or unknown risks or uncertainties materialize, actual results could vary materially from the expectations and projections of Janssen Biotech, Inc., Janssen Research & Development, LLC, any of the other Janssen Pharmaceutical Companies, and/or Johnson & Johnson. Risks and uncertainties include, but are not limited to: challenges and uncertainties inherent in product research and development, including the uncertainty of clinical success and of obtaining regulatory approvals; uncertainty of commercial success; manufacturing difficulties and delays; competition, including technological advances, new products and patents attained by competitors; challenges to patents; product efficacy or safety concerns resulting in product recalls or regulatory action; changes in behavior and spending patterns of purchasers of health care products and services; changes to applicable laws and regulations, including global health care reforms; and trends toward health care cost containment. A further list and descriptions of these risks, uncertainties and other factors can be found in Johnson & Johnson's Annual Report on Form 10-K for the fiscal year ended January 1, 2023, including in the sections captioned "Cautionary Note Regarding Forward-Looking Statements" and "Item 1A. Risk Factors," and in Johnson & Johnson's subsequent Quarterly Reports on Form 10-Q and other filings with the Securities and Exchange Commission. Copies of these filings are available online at [www.sec.gov](http://www.sec.gov), [www.jnj.com](http://www.jnj.com) or on request from Johnson & Johnson. None of the Janssen Pharmaceutical Companies nor Johnson & Johnson undertakes to update any forward-looking statement as a result of new information or future events or developments.*

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- <sup>12</sup> IMBRUVICA® U.S. Prescribing Information, August 2022.