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U.S. FDA Approves IMBRUVICA® (ibrutinib) Plus Obinutuzumab as First Non-Chemotherapy Combination Regimen for Treatment-Naïve Patients with Chronic Lymphocytic Leukemia

- *Patients treated with IMBRUVICA plus obinutuzumab experienced a 77 percent reduction in risk of progression or death compared to chlorambucil plus obinutuzumab*
- *Approval broadens the label in frontline CLL and represents the tenth FDA approval for IMBRUVICA*
- *IMBRUVICA label now includes additional monotherapy long-term follow-up data*

HORSHAM, PA, January 28, 2019 – The Janssen Pharmaceutical Companies of Johnson & Johnson announced today the U.S. Food and Drug Administration (FDA) approval of IMBRUVICA® (ibrutinib) in combination with obinutuzumab in treatment-naïve patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), the most common form of leukemia in adults.[1] This is the first approval for a non-chemotherapy combination regimen for treatment-naïve patients with CLL/SLL, and marks the tenth FDA approval for IMBRUVICA since its U.S. launch in November 2013. The approval expands the label for IMBRUVICA in frontline CLL/SLL beyond its use as a monotherapy to include combination

use with obinutuzumab. IMBRUVICA, a Bruton's tyrosine kinase (BTK) inhibitor, is jointly developed and commercialized by Janssen Biotech, Inc. and Pharmacyclics LLC, an AbbVie company.

"In just a few years, IMBRUVICA has become an important treatment for chronic lymphocytic leukemia. IMBRUVICA as a single agent – and now as a combination with obinutuzumab – provides patients with CLL with an alternative to frontline treatment with chemoimmunotherapy," said Carol Moreno, M.D., Ph.D., Consultant Hematologist, Hospital de la Santa Creu Sant Pau, Autonomous University of Barcelona, Barcelona, Spain, and lead investigator of the iLLUMINATE study.

This approval is based on results from the Phase 3 iLLUMINATE study (PCYC-1130). At a median follow-up of 31 months, IMBRUVICA plus obinutuzumab showed a significant improvement in Independent Review Committee (IRC)-evaluated progression-free survival compared with chlorambucil plus obinutuzumab (median not evaluable [NE] vs. 19 months; hazard ratio [HR] 0.23; 95 percent confidence interval [CI]: 0.15-0.37; P<0.0001), with a 77 percent reduction in risk of progression or death. Patients with high-risk disease (17p deletion/TP53 mutation, 11q deletion, or unmutated IGHV) treated with IMBRUVICA plus obinutuzumab experienced an 85 percent reduction in risk of progression or death (HR 0.15; 95 percent CI: 0.09-0.27). The IRC-evaluated overall response rate was 89 percent in the IMBRUVICA plus obinutuzumab arm versus 73 percent in the chlorambucil plus obinutuzumab arm. The data were recently presented in an oral session at the 2018 American Society of Hematology (ASH) Annual Meeting and simultaneously published in *The Lancet Oncology*.

"This label update builds upon the established efficacy and safety of IMBRUVICA in the frontline treatment of patients with CLL/SLL, as a monotherapy or in combination with other treatments," said Craig Tendler, M.D., Vice President, Clinical Development and Global Medical Affairs, Janssen Research & Development, LLC. "This milestone represents our continued commitment to develop IMBRUVICA-based, non-chemotherapy regimens to address the clinical needs of patients living with CLL/SLL."

The FDA also updated the IMBRUVICA label to include additional long-term efficacy data supporting its use as a monotherapy in CLL/SLL, with approximately five years of follow-up

from the Phase 3 RESONATE™ (PCYC-1112) and RESONATE™-2 (PCYC-1115, PCYC-1116) international studies.

Warnings and Precautions include hemorrhage, infections, cytopenias, cardiac arrhythmias, hypertension, second primary malignancies, tumor lysis syndrome, and embryo-fetal toxicity. The most common adverse reactions (occurring in 20 percent or more of patients) of all grades in patients treated with IMBRUVICA plus obinutuzumab in the iLLUMINATE study were neutropenia (48 percent), thrombocytopenia (36 percent), rash (36 percent), diarrhea (34 percent), musculoskeletal pain (33 percent), bruising (32 percent), cough (27 percent), infusion related reaction (25 percent), hemorrhage (25 percent), and arthralgia (22 percent).

The recommended dose of IMBRUVICA for CLL/SLL is 420 mg orally once daily until disease progression or unacceptable toxicity as a single agent or in combination with obinutuzumab or bendamustine and rituximab (BR). When administering IMBRUVICA in combination with rituximab or obinutuzumab, doctors should consider administering IMBRUVICA prior to rituximab or obinutuzumab when given on the same day.

About IMBRUVICA

IMBRUVICA (ibrutinib) is a once-daily oral medicine that works differently than chemotherapy as it blocks the Bruton's tyrosine kinase (BTK) protein. The BTK protein sends important signals that tell B cells to mature and produce antibodies. BTK signaling is needed by specific cancer cells to multiply and spread.[2,3] By blocking BTK, IMBRUVICA may help move abnormal B cells out of their nourishing environments in the lymph nodes, bone marrow, and other organs.[4,5]

IMBRUVICA is approved in more than 90 countries, and, to date, has been used to treat more than 135,000 patients worldwide across approved indications. It was first approved by the U.S. Food and Drug Administration (FDA) in November 2013, and today is indicated in six disease areas, including five hematologic cancers – chronic lymphocytic leukemia (CLL) with or without 17p deletion (del17p), small lymphocytic lymphoma (SLL) with or without del17p, Waldenström's macroglobulinemia (WM), previously-treated patients with mantle cell lymphoma (MCL)*, previously-treated patients with marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy* – and previously-treated patients with chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy.[5]

IMBRUVICA is the first and only FDA-approved medicine in WM, MZL* and cGVHD. IMBRUVICA has been granted four Breakthrough Therapy Designations by the FDA, and it was one of the first medicines to receive U.S. approval through the Breakthrough Therapy Designation.

** Accelerated approval was granted for MCL and MZL based on overall response rate. Continued approval for MCL and MZL may be contingent upon verification and description of clinical benefit in confirmatory trials.*

IMBRUVICA is a comprehensively studied molecule in the oncology industry. The robust clinical oncology development program includes more than 150 active clinical trials studying IMBRUVICA alone and in combination with other medicines in several blood cancers and other serious diseases. For more information, visit www.IMBRUVICA.com.

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 3% of patients, with fatalities occurring in 0.3% of 1,124 patients exposed to IMBRUVICA® in clinical trials. Bleeding events of any grade, including bruising and petechiae, occurred in 44% 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 24% of 1,124 patients exposed to 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.

Cytopenias: Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (23%), thrombocytopenia (8%), and anemia (3%) 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 0.2% of patients, and Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4% of 1,124 patients exposed to IMBRUVICA® in clinical trials. 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 of any grade occurred in 12% of 1,124 patients treated with IMBRUVICA® in clinical trials. Grade 3 or greater hypertension occurred in 5% of patients with a median time to onset of 5.9 months (range, 0.03 to 24 months).

Monitor blood pressure in patients treated with IMBRUVICA® and initiate or adjust anti-hypertensive medication throughout treatment with IMBRUVICA® as appropriate.

Second Primary Malignancies: Other malignancies (10%) including non-skin carcinomas (4%) have occurred in 1,124 patients treated with 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® 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 (58%)*, diarrhea (41%), anemia (38%)*, neutropenia (35%)*, musculoskeletal pain (32%), rash (32%), bruising (31%), nausea (26%), fatigue (26%), hemorrhage (24%), and pyrexia (20%).

The most common Grade 3 or 4 adverse reactions (≥5%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia (18%)*, thrombocytopenia (16%)*, and pneumonia (14%).

Approximately 7% (CLL/SLL), 14% (MCL), 14% (WM) and 10% (MZL) of 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 (≥20%) in patients with cGVHD were fatigue (57%), bruising (40%), diarrhea (36%), thrombocytopenia (33%)*, muscle spasms (29%), stomatitis (29%), nausea (26%), hemorrhage (26%), anemia (24%)*, and pneumonia

(21%).

The most common Grade 3 or higher adverse reactions (≥5%) reported in patients with cGVHD were pneumonia (14%), fatigue (12%), diarrhea (10%), neutropenia (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.

DRUG INTERACTIONS

CYP3A Inhibitors: Modify IMBRUVICA® dose as described in USPI sections 2.4 and 7.1.

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 click here for full Prescribing Information.

About the Janssen Pharmaceutical Companies of Johnson & Johnson

At the Janssen Pharmaceutical Companies of Johnson & Johnson, we are working to create a world without disease. Transforming lives by finding new and better ways to prevent, intercept, treat and cure disease inspires us. We bring together the best minds and pursue the most promising science. We are Janssen. We collaborate with the world for the health of everyone in it. Learn more at www.janssen.com. Follow us at @JanssenUS and @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 a new improved indication for 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., 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 December 31, 2017, including in the sections captioned "Cautionary Note Regarding Forward-Looking Statements" and "Item 1A. Risk Factors," and in the company's most recently filed Quarterly Report on Form 10-Q and the company's subsequent filings with the Securities and Exchange Commission. Copies of these filings are available online at www.sec.gov, www.jnj.com or on request from Johnson & Johnson. Neither 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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[1] American Cancer Society. What Is Chronic Lymphocytic Leukemia? https://www.cancer.org/cancer/chronic-lymphocytic-leukemia/about/what-is-cll.html. Accessed January 2019.
[2] Genetics Home Reference. Isolated growth hormone deficiency. http://ghr.nlm.nih.gov/condition/isolated-growth-hormone-deficiency. Accessed January 2019.
[3] Turetsky, et al. Single cell imaging of Bruton's Tyrosine Kinase using an irreversible inhibitor. Scientific Reports. volume 4, Article number: 4782 (2014).
[4] de Rooij MF, Kuil A, Geest CR, et al. The clinically active BTK inhibitor PCI-32765 targets B-cell receptor- and chemokine-controlled adhesion and migration in chronic lymphocytic leukemia. Blood. 2012;119(11):2590-2594.
[5] IMBRUVICA U.S. Prescribing Information, January 2019.