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U.S. FDA Approves IMBRUVICA® (ibrutinib) Plus Rituximab as First Non-Chemotherapy Combination Regimen for Patients with Waldenström's Macroglobulinemia, a Rare Blood Cancer

- *Latest FDA approval expands label for IMBRUVICA, the only BTK inhibitor indicated for Waldenström's macroglobulinemia (WM)*
- *IMBRUVICA plus rituximab showed significant improvement in progression-free survival at 30 months and demonstrated superiority versus rituximab monotherapy in WM*

HORSHAM, Pa., August 27, 2018 – The Janssen Pharmaceutical Companies of Johnson & Johnson today announced the U.S. Food and Drug Administration (FDA) approval of IMBRUVICA® (ibrutinib) in combination with rituximab for the treatment of Waldenström's macroglobulinemia (WM), a rare blood cancer.[1] The approval expands the label for IMBRUVICA in WM beyond its current approved use as a monotherapy to include combination use with rituximab. This approval represents the first approved non-chemotherapy combination option for the treatment of WM. IMBRUVICA first received FDA approval in WM as a monotherapy in January 2015 via the Breakthrough Therapy Designation pathway, making it the first FDA-approved therapy for the disease. The expanded label marks the ninth FDA approval for IMBRUVICA since 2013. IMBRUVICA is a first-in-class Bruton's tyrosine kinase (BTK) inhibitor jointly developed and commercialized by Janssen Biotech, Inc. and Pharmacyclics LLC, an AbbVie company.

“The combination of IMBRUVICA and rituximab provides health care professionals with a new treatment option for patients living with this serious blood cancer,” said Dr. Lia Palomba, hematologist-oncologist at Memorial Sloan-Kettering Cancer Center, New York, and iNNOVATE study investigator. “Before IMBRUVICA, there were no FDA-approved treatment options for patients with Waldenström’s macroglobulinemia, a disease first acknowledged nearly 75 years ago. Today, IMBRUVICA continues to provide an important therapeutic approach in the treatment of this complex disease.”

This approval is based on results from the randomized, double-blind, placebo-controlled iNNOVATE study (PCYC-1127), the largest Phase 3 study of a non-chemotherapy combination in WM patients. The iNNOVATE study evaluated IMBRUVICA in combination with rituximab versus placebo plus rituximab in 150 patients with either relapsed/refractory (r/r) disease or previously untreated WM. At a median follow up of 26.5 months, a significant improvement in the Independent Review Committee (IRC)-assessed primary endpoint of progression-free survival (PFS) was seen with IMBRUVICA plus rituximab when compared with placebo plus rituximab (30-month PFS rates were 82% vs. 28%, respectively). Patients in the IMBRUVICA plus rituximab treatment arm experienced an 80% reduction in relative risk of disease progression or death compared with patients treated with placebo plus rituximab (hazard ratio=0.20; confidence interval, 0.11-0.38, p<0.0001). The data were presented in an oral session at the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting, selected for Best of ASCO 2018 Meetings, and simultaneously published in *The New England Journal of Medicine*.

“Results from iNNOVATE showed significant improvement in progression-free survival at 30 months and demonstrated the superiority of IMBRUVICA plus rituximab over rituximab monotherapy in Waldenström's macroglobulinemia,” said Meletios A. Dimopoulos, M.D., Professor and Chairman of the Department of Clinical Therapeutics, National and Kapodistrian University of Athens School of Medicine, Athens, Greece, and iNNOVATE lead study investigator. “Based on these results, IMBRUVICA in combination with rituximab may be considered as a first- and second-line option for appropriate people diagnosed and living with WM.”

“The clinical data generated for IMBRUVICA plus rituximab in the treatment of Waldenström’s macroglobulinemia offers physicians evidence to consider this combination regimen for newly-diagnosed patients. Today’s approval represents an important milestone for people living with this rare and incurable blood cancer who have limited FDA-approved treatment options,” said Andree Amelsberg, M.D., Vice President of Oncology Medical Affairs at Janssen Scientific Affairs, LLC. “We remain dedicated to a comprehensive clinical development program to explore the full potential of IMBRUVICA, including in combination with other therapies.”

Warnings and Precautions remain the same: hemorrhage, infections, cytopenias, cardiac arrhythmias, hypertension, second primary malignancies, tumor lysis syndrome, and embryo-fetal toxicity. The most common adverse reactions (occurring in 20% or more of patients) of all grades in patients treated with IMBRUVICA plus rituximab in the iNNOVATE study were bruising (37%), musculoskeletal pain (35%), hemorrhage (32%), diarrhea (28%), rash (24%), arthralgia (24%), nausea (21%), and hypertension (20%). Grade 3 or 4 infusion-related reactions were observed in 1% of patients treated with IMBRUVICA plus rituximab.

The recommended dose of IMBRUVICA for WM is 420 mg orally once daily until disease progression or unacceptable toxicity as a single agent or in combination with rituximab. When administering IMBRUVICA in combination with rituximab, consider administering IMBRUVICA prior to rituximab when given on the same day.

About Waldenström's Macroglobulinemia (WM)

WM is a rare, slow-growing and incurable form of non-Hodgkin lymphoma (NHL) with limited FDA-approved treatment options. WM typically affects older adults and is primarily found in the bone marrow, although lymph nodes and the spleen also may be affected. In the U.S., there are about 2,800 new cases of WM each year.[1]

About IMBRUVICA

IMBRUVICA (ibrutinib) is a first-in-class, once-daily oral medicine that works differently than chemotherapy and immunotherapy treatments as it blocks the Bruton's tyrosine kinase (BTK) protein. The BTK protein sends important signals that cause B cells to abnormally mature and multiply.[2] IMBRUVICA targets and blocks BTK, inhibiting the survival and spread of cancer cells, and can interfere with the disease process of other serious conditions.

IMBRUVICA was first approved by the U.S. Food and Drug Administration in 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 mantle cell lymphoma (MCL)*, previously-treated marginal zone lymphoma (MZL)* – and previously-treated chronic graft-versus-host disease (cGVHD).[3] 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 pathway. IMBRUVICA is approved in more than 90 countries, and, to date, has been used to treat approximately 115,000 patients worldwide across approved indications.[4]

IMBRUVICA is one of the most comprehensively studied molecules in the 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.

** 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.*

Additional Information about IMBRUVICA®

INDICATIONS

IMBRUVICA is indicated to treat adults with[3]

- 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 3% of patients, with fatalities occurring in 0.3% of 1,011 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 1,011 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 1,011 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 has occurred in 12% of 1,011 patients treated with IMBRUVICA® in clinical trials with a median time to onset of 5 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 (9%) including non-skin carcinomas (2%) have occurred in 1,011 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%)*, neutropenia (58%)*, diarrhea (42%), anemia (39%)*, rash (31%), musculoskeletal pain (31%), bruising (31%), nausea (28%), fatigue (27%), hemorrhage (23%), 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 (36%)*, thrombocytopenia (15%)*, and pneumonia (10%).

Approximately 6% (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%)*, 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 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 www.twitter.com/JanssenGlobal and www.twitter.com/JanssenUS. Janssen Biotech, Inc. and Janssen Scientific Affairs, 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 Janssen Pharmaceutical Companies of Johnson & Johnson 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 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, 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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[1] Lymphoma Research Foundation. Getting the facts: Waldenström macroglobulinemia. https://www.lymphoma.org/wp-content/uploads/2017/06/LRF_FACTSHEET_Waldenstro%CC%88m_Macroglobulinemia.pdf. Accessed August 2018.
[2] Genetics Home Reference. Isolated growth hormone deficiency. http://ghr.nlm.nih.gov/condition/isolated-growth-hormone-deficiency. Accessed August 2018.
[3] IMBRUVICA U.S. Prescribing Information, August 2018.
[4] Janssen Global Services, LLC. Data on file. 2018.