**Media Inquiries:**
Bernadette King
Phone: 1-215-778-3027

Satu Glawe
Phone: +49 172 294 6264

**Investor Relations:**
Christopher DelOrefice
Phone: 1-732-524-2955

Lesley Fishman
Phone: 1-732-524-3922

**U.S. Medical Inquiries:**
1-800-526-7736

# Janssen Announces Submission of Supplemental New Drug Application to U.S. FDA Seeking Approval of IMBRUVICA® (ibrutinib) in Combination with Rituximab for Previously Untreated Patients with Chronic Lymphocytic Leukemia

*Supplemental New Drug Application – submitted through FDA Real-Time Oncology Review program – is based on positive Phase 3 data in patients aged 70 or younger*

RARITAN, NJ, November 8, 2019 – The Janssen Pharmaceutical Companies of Johnson & Johnson announced today the submission of a supplemental New Drug Application (sNDA) to the U.S. Food and Drug Administration (FDA) seeking approval to expand the IMBRUVICA® (ibrutinib) label to include the combination with rituximab for the first-line treatment of patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). The submission is based on positive results from the investigational Phase 3 E1912 study designed and conducted by the ECOG-ACRIN Cancer Research Group (ECOG-ACRIN) and sponsored by the National Cancer Institute (NCI), which is part of the National Institutes of Health. The study met the primary endpoints of progression-free survival (PFS) and overall survival (OS) in patients aged 70 years or younger treated with IMBRUVICA plus rituximab, compared to the chemoimmunotherapy regimen of fludarabine,

cyclophosphamide and rituximab (FCR). Results from the study were presented at the 2018 American Society of Hematology (ASH) Annual Meeting and were recently published in *The New England Journal of Medicine* August 2019 issue.

"ECOG-ACRIN's E1912 is a landmark head-to-head clinical trial of an IMBRUVICA-based regimen versus FCR, the most common chemoimmunotherapy regimen established to date for the frontline treatment of younger adult patients with CLL," said Craig Tendler, M.D., Vice President, Clinical Development and Global Medical Affairs, Janssen Research & Development, LLC. "We look forward to working closely with the FDA to bring this new IMBRUVICA-based chemotherapy-free option to younger adult CLL patients based on the significant delay in disease progression and survival benefit as demonstrated in the E1912 study."

The sNDA is being reviewed by the U.S. FDA under the Real-Time Oncology Review (RTOR) pilot program. The program is designed to explore a more efficient review process, ensuring safe and effective treatments become available to patients earlier, while maintaining quality of review.

IMBRUVICA is a once-daily, first-in-class Bruton's tyrosine kinase (BTK) inhibitor that is administered orally, and is jointly developed and commercialized by Janssen Biotech, Inc. and Pharmacyclics LLC, an AbbVie company.

**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.[1,2] By blocking BTK, IMBRUVICA may help move abnormal B cells out of their nourishing environments in the lymph nodes, bone marrow, and other organs.[3]

IMBRUVICA is approved in more than 95 countries for at least one indication, and, to date, has been used to treat more than 170,000 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.[4]

** 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.*

As of early 2019, the National Comprehensive Cancer Network® (NCCN®), a not-for-profit alliance of 28 leading cancer centers devoted to patient care, research, and education, recommends ibrutinib (IMBRUVICA®) as a preferred regimen for the initial treatment of CLL/SLL, and it is the only Category 1 single-agent regimen for treatment-naïve patients without deletion 17p. IMBRUVICA is the only FDA-approved medicine in WM 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 with the Breakthrough Therapy Designation.

IMBRUVICA is a comprehensively studied molecule, with 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®. 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) have occurred in 4% of patients, with fatalities occurring in 0.4% of 2,838 patients exposed to IMBRUVICA® in 27 clinical trials. Bleeding events of any grade, including bruising and petechiae, occurred in 39% of patients treated with IMBRUVICA®.

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. In IMBRUVICA® clinical trials, 3.1% of patients taking 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 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:** Co-administration of IMBRUVICA® with strong or moderate CYP3A inhibitors may increase ibrutinib plasma concentrations. Dose modifications of IMBRUVICA® may be recommended when used concomitantly with posaconazole, voriconazole, and moderate CYP3A inhibitors. Avoid concomitant use of other strong CYP3A inhibitors. Interrupt IMBRUVICA® if strong inhibitors are used short-term (e.g., for ≤ 7 days). See dose modification guidelines 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 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, Immunology, Infectious Diseases & Vaccines, Neuroscience, Oncology, and Pulmonary Hypertension.

Learn more at www.janssen.com. Follow us at www.twitter.com/JanssenGlobal and www.twitter.com/JanssenUS. Janssen Research & Development, LLC and Janssen Biotech, Inc. are members 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 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 December 30, 2018, 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. 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.*

**# # #**

---

[1] Genetics Home Reference. Isolated growth hormone deficiency. http://ghr.nlm.nih.gov/condition/isolated-growth-hormone-deficiency. Accessed November 2019.

[2] Turetsky, A, et al. Single cell imaging of Bruton's Tyrosine Kinase using an irreversible inhibitor. Scientific Reports. volume 4, Article number: 4782 (2014).

[3] 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.

[4] IMBRUVICA U.S. Prescribing Information, September 2019.