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Johnson & Johnson Announces Expansion of IMBRUVICA® (ibrutinib) Label in the U.S. to Include Oral Suspension Formulation for Adult Patients in its Approved Indications

IMBRUVICA® is now the only Bruton's tyrosine kinase inhibitor (BTKi) approved with an oral suspension formulation, providing additional flexibility for patients who may have difficulty swallowing tablets or capsules

HORSHAM, PA. (February 26, 2024) – Johnson & Johnson, in collaboration with its alliance partner, Pharmacyclics LLC, an AbbVie Company, announced today that the U.S. Food and Drug Administration (FDA) has approved a label expansion for IMBRUVICA® (ibrutinib) with an oral suspension formulation for adult patients in the treatment of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL); Waldenström's macroglobulinemia (WM); and chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy.

"Some patients may have trouble swallowing medications, adding another layer of complexity to their treatment journey," said Lisa Nodzon, PhD, ARNP, AOCNP at Moffitt Cancer Center.‡ "Having multiple formulations of IMBRUVICA offers prescribers another option when treating adults with CLL/SLL, WM, or cGVHD, which could make a difference in their daily lives."

Data show that an estimated five percent of patients treated with a Bruton's tyrosine kinase inhibitor (BTKi) for CLL or WM have potential difficulty swallowing.[1] The oral suspension formulation of IMBRUVICA® provides a benefit compared to other BTKis, offering flexible administration with more options for patients and providers.

"As the most comprehensively studied therapy in its class, IMBRUVICA has helped change the standard of care for adults living with certain blood cancers and cGVHD. Nearly 300,000 patients worldwide have been treated with IMBRUVICA to date, and we're continually looking toward the future to help support additional patients," said Mark Wildgust, PhD, Vice President, Global Medical Affairs, Oncology, Johnson & Johnson Innovative Medicine. "The approval of an IMBRUVICA oral suspension formulation underscores our commitment in providing innovative, alternate delivery options that address individualized patient needs and allow patients flexibility in how they take their medicine."

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 inhibit their proliferation.[2,3,4]

IMBRUVICA® is approved in more than 100 countries and has been used to treat almost 300,000 patients worldwide over the last decade. There are more than 50 company-sponsored clinical trials, including 18 Phase 3 studies, spanning 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. 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.[5]

IMPORTANT SAFETY INFORMATION

INDICATIONS
IMBRUVICA® is a kinase inhibitor indicated for the treatment of:

- Adult patients with chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL).
- Adult patients with chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL) with 17p deletion.
- Adult patients with Waldenström's macroglobulinemia (WM).

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- Adult and pediatric patients age 1 year and older with chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy.

For more information, visit www.IMBRUVICA.com.

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 with B-cell malignancies 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 with B-cell malignancies who received IMBRUVICA® in clinical trials. Grade 3 or greater hypertension occurred in 8% of patients. Based on data from a subset of these patients, (N=1,124), the median time to onset was 5.9 months (range, 0 to 24 months). In a long-term safety analysis over 5 years of 1,284 patients with B-cell malignancies treated for a median of 36 months (range, 0 to 98 months), the cumulative rate of hypertension increased over time. The prevalence for Grade 3 or greater hypertension was 4% (year 0-1), 7% (year 1-2), 9% (year 2-3), 9% (year 3-4), and 9% (year 4-5); the overall incidence for the 5-year period was 11%. Monitor blood pressure in

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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 with B-cell malignancies 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 (≥30%) in adult patients with B-cell malignancies were thrombocytopenia (55%)*, diarrhea (44%), fatigue (39%), musculoskeletal pain (39%), neutropenia (39%)*, rash (36%), anemia (35%)*, bruising (32%), and nausea (30%).

The most common Grade ≥ 3 adverse reactions (≥5%) in adult patients with B-cell malignancies were neutropenia (21%)*, thrombocytopenia (14%)*, pneumonia (8%), and hypertension (8%).

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

cGVHD: The most common adverse reactions (≥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 (≥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® 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® 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® are 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). Avoid grapefruit and Seville oranges during IMBRUVICA® 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.

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SPECIFIC POPULATIONS

Pediatric Use: The safety and effectiveness of IMBRUVICA® have not been established for the treatment of cGVHD after failure of one or more lines of therapy in pediatric patients less than 1 year of age. The safety and effectiveness of IMBRUVICA® in pediatric patients have not been established in CLL/SLL, CLL/SLL with 17p deletion, WM, or in patients with mature B-cell non-Hodgkin lymphoma.

In the randomized population from a study that included 35 patients (26 pediatric patients age 5 to less than 17 years) with previously treated mature B-cell non-Hodgkin lymphoma, 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 Johnson & Johnson

At Johnson & Johnson, we believe health is everything. Our strength in healthcare innovation empowers us to build a world where complex diseases are prevented, treated, and cured, where treatments are smarter and less invasive, and solutions are personal. Through our expertise in Innovative Medicine and MedTech, we are uniquely positioned to innovate across the full spectrum of healthcare solutions today to deliver the breakthroughs of tomorrow, and profoundly impact health for humanity. Learn more at https://www.jnj.com/ or at https://www.janssen.com/johnson-johnson-innovative-medicine. Follow us at @JanssenUS and @JNJInnovMed. Janssen Research & Development, LLC, Janssen Biotech, Inc. and Janssen Global Services, LLC are Johnson & Johnson companies.

Cautions Concerning Forward-Looking Statements

This press release contains "forward-looking statements" as defined in the Private Securities Litigation Reform Act of 1995 regarding development of 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, Janssen Biotech, Inc., Janssen Global Services, LLC 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; competition, including technological advances, new products and patents attained by competitors; challenges to patents; 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, 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, www.jnj.com or on request from Johnson & Johnson. None of Janssen Research & Development, LLC, Janssen Biotech, Inc., Janssen Global Services, LLC 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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‡*Lisa Nodzon has provided consulting, advisory, and speaking services to Johnson & Johnson; she has not been paid for any media work.*

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1 IQVIA Market Sizing Data, October 2022-September 2023.
2 Genetics Home Reference. Isolated growth hormone deficiency. http://ghr.nlm.nih.gov/condition/isolated-growth-hormone-deficiency.
3 Turetsky A, et al. Single cell imaging of Bruton's tyrosine kinase using an irreversible inhibitor. *Scientific Reports*. 2014;6:4782.
4 de Rooij MF, 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, February 2024.