

**News Release**

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**U.S. FDA Approves IMBRUVICA® (ibrutinib) as First and Only BTKi Treatment for Pediatric Patients with Chronic Graft-Versus-Host Disease**

*IMBRUVICA® is now the only BTKi with 12 FDA approvals across seven indications, including five hematologic cancers and cGVHD*

**August 24, 2022 (HORSHAM, PA)** – The Janssen Pharmaceutical Companies of Johnson & Johnson announced today that the U.S. Food and Drug Administration (FDA) has approved IMBRUVICA® (ibrutinib) for the treatment of pediatric patients one year and older with chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy. This milestone marks the first pediatric indication for IMBRUVICA® and the introduction of a new oral suspension formulation for patients ages one to less than 12. IMBRUVICA® is now the first FDA-approved therapy for these younger patients who previously had no approved treatment options for this life-threatening disease.

Chronic graft-versus-host disease is a life-threatening complication that can occur after a stem cell or bone marrow transplant when newly transplanted donor cells attack the transplant recipient's body.<sup>1</sup> Symptoms may include skin rash, mouth sores, dry eyes, liver inflammation, development of scar tissue in the skin and joints, and damage to the lungs.<sup>1</sup> Among children who undergo allogeneic transplants, 52-65 percent will develop cGVHD.<sup>2</sup>

“Imagine going through a transplant and then being told you have a moderate to severe chronic disease that can sometimes also be life-threatening,” said Dr. Paul A. Carpenter, attending physician at Seattle Children's Hospital and a study principal investigator.<sup>†</sup> “If these children were between one and 12 and didn’t respond to steroid treatment, we didn’t have any rigorously studied treatment options — until now. The iMAGINE trial showed encouraging safety results and sustained response rates in children, and the new IMBRUVICA oral suspension formulation helps address challenges children may have with swallowing capsules or tablets.”

“It’s heartbreaking for parents to watch their child struggle with the debilitating effects of cGVHD, especially since there are so few treatment options,” said Susan Stewart, Executive Director of BMT InfoNet,<sup>^</sup> a non-profit organization dedicated to providing patients and their loved ones with emotional support and high quality, easy-to-understand information about blood stem cell transplants. “The FDA approval of IMBRUVICA puts another weapon in their arsenal and has the potential to truly make a difference for those who are faced with this challenging disease.”

The new indication is based on results from the Phase 1/2 iMAGINE study, which showed an overall response rate (ORR) through week 25 of 60 percent (Confidence Interval [CI] 95 percent; 44-74) in patients median age 13 years (range, one to 19 years) (n=47) with relapsed/refractory (R/R) moderate to severe cGVHD. Safety was consistent with the established profile for IMBRUVICA<sup>®</sup>, with observed adverse events (AEs) in pediatric patients being consistent with those observed in adult patients with moderate to severe cGVHD. IMBRUVICA<sup>®</sup> was approved to treat adults with cGVHD after failure of one or more lines of systemic therapy in 2017. Because of its unique kinase profile (e.g., inhibiting both BTK and interleukin-2-inducible T-cell kinase [ITK]), IMBRUVICA<sup>®</sup> has the potential to provide a clinical benefit for cGVHD.<sup>3</sup>

“The pediatric cGVHD community is a prime example of an underserved patient population with high unmet medical needs for whom Janssen is committed to developing life-saving therapies,” said Craig Tandler, M.D., Global Head of Late Development, Diagnostics & Medical Affairs, Hematology & Oncology Janssen Research & Development, LLC. “cGVHD has life-threatening implications for children, and we are deeply proud of the opportunity to make an impact for these young patients with IMBRUVICA and their families.”

### **About the iMAGINE Study**

iMAGINE ([PCYC-1146-IM](#)) is an open-label, multi-center, single-arm trial of IMBRUVICA® for the treatment of pediatric and young adult patients aged one year to less than 22 years with moderate or severe cGVHD as defined by NIH Consensus Criteria. Primary endpoints included pharmacokinetics (PK) and safety, and secondary endpoints included ORR (complete response [CR]/partial response [PR]) per 2014 NIH criteria, overall survival, and duration of response (DOR). The study included 47 patients who required additional therapy after failure of one or more prior lines of systemic therapy. Patients aged 12 years and older were treated with IMBRUVICA® 420 mg orally once daily, and patients aged one year to less than 12 years were treated with IMBRUVICA® 240 mg/m<sup>2</sup> orally once daily. The efficacy of IMBRUVICA® was established based on ORR through Week 25.

### **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 Bruton's tyrosine kinase (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>4,5,6</sup>

IMBRUVICA® is approved in more than 100 countries and has been used to treat more than 250,000 patients worldwide. There are more than 50 company-sponsored clinical trials, including 18 Phase 3 studies, more than 11 years evaluating the efficacy and safety of IMBRUVICA®.

IMBRUVICA® was first approved by the U.S. Food and Drug Administration (FDA) in November 2013, and today is indicated for adult patients in six disease areas, including five hematologic cancers. These include indications to treat adults with chronic lymphocytic leukemia (CLL)/ small lymphocytic lymphoma (SLL) with or without 17p deletion (del17p), and adults with Waldenström's macroglobulinemia (WM), and adult patients with previously treated mantle cell lymphoma (MCL)\*, as well as to treat adult patients with previously treated marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy\*, 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>7</sup>

*\*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.*

Since 2019, the National Comprehensive Cancer Network<sup>®</sup> (NCCN<sup>®</sup>), recommends ibrutinib (IMBRUVICA<sup>®</sup>) as a preferred regimen for the initial treatment of CLL/SLL and has Category 1 treatment status for treatment-naïve patients without deletion 17p/*TP53* mutation and as a preferred treatment for treatment-naïve patients with deletion 17p/*TP53* mutation. The NCCN Guidelines<sup>®</sup> also recommend IMBRUVICA<sup>®</sup>, with or without rituximab, as a preferred regimen for the treatment of relapsed/refractory MCL, as a Category 1 preferred regimen for both untreated and previously treated WM patients, and as a preferred regimen for relapsed/refractory MZL.<sup>8</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<sup>®</sup>. Major hemorrhage ( $\geq$  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<sup>®</sup> 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<sup>®</sup>, respectively.

The mechanism for the bleeding events is not well understood.

Use of either anticoagulant or antiplatelet agents concomitantly with IMBRUVICA<sup>®</sup> increases the risk of major hemorrhage. Across clinical trials, 3.1% of 2,838 patients who received IMBRUVICA<sup>®</sup> 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 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.

## **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 MCL, CLL/SLL, CLL/SLL with 17p deletion, WM, MZL 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 see full [Prescribing Information](#).**

*†Dr. Carpenter has served as a paid consultant to Janssen; he has not been paid for any media work.*

*^Janssen Biotech, Inc. provides sponsorship funding to BMT InfoNet. Susan Stewart has not been paid for any media work.*

### **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 [www.twitter.com/JanssenGlobal](https://www.twitter.com/JanssenGlobal) and [www.twitter.com/JanssenUS](https://www.twitter.com/JanssenUS). Janssen Research and Development, LLC and Janssen Biotech, Inc. 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 product development and the potential benefits and treatment impact 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 or 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 2, 2022, 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](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>1</sup> National Center for Advancing Translational Sciences. Chronic Graft Versus Host Disease.

<https://rarediseases.info.nih.gov/diseases/10964/chronic-graft-versus-host-disease>. Accessed August 2022.

<sup>2</sup> Sobkowiak-Sobierajska A. et al. Management of Chronic Graft-vs.-Host Disease in Children and Adolescents With ALL: Present Status and Model for a Personalised Management Plan. *Front. Pediatr.* 2022;10:2296-2360. Accessed August 2022.

<sup>3</sup> Miklos D., et al. Ibrutinib for chronic graft-versus-host disease after failure of prior therapy. *Blood.* 2017; 130:2243-2244.

<sup>4</sup> Genetics Home Reference. Isolated growth hormone deficiency. <http://ghr.nlm.nih.gov/condition/isolated-growth-hormone-deficiency>. Accessed August 2022.

<sup>5</sup> Turetsky A, et al. Single cell imaging of Bruton's tyrosine kinase using an irreversible inhibitor. *Scientific Reports.* 2014;6:4782.

<sup>6</sup> 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.

<sup>7</sup> IMBRUVICA<sup>®</sup> U.S. Prescribing Information, August 2022.

<sup>8</sup> NCCN<sup>®</sup> Clinical Practice Guidelines in Oncology (NCCN Guidelines<sup>®</sup>) for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma V2.2022. National Comprehensive Cancer Network. Accessed August 2022.