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IMBRUVICA™ (ibrutinib) Capsules Now Approved in the U.S. for Mantle Cell Lymphoma Patients Who Have Received at Least One Prior Therapy

Single-agent oral therapy is one of the first medications to be approved via the U.S. Food and Drug Administration's Breakthrough Therapy Designation Pathway

HORSHAM, PA, NOVEMBER 13, 2013 – Janssen Biotech, Inc. [“Janssen”] today announced the U.S. Food and Drug Administration (FDA) has approved IMBRUVICA™ (ibrutinib) capsules for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.¹ This indication is based on overall response rate (ORR). An improvement in survival or disease-related symptoms has not been established.

IMBRUVICA is one of the first medications to receive FDA approval via the Breakthrough Therapy Designation pathway. Its approval comes just more than four months after the New Drug Application (NDA) submission was completed in late June 2013. IMBRUVICA is being jointly developed and commercialized by Janssen and Pharmacylics, Inc.

“Mantle cell lymphoma is a rare, aggressive type of B-cell lymphoma,” said Michael Wang, M.D., Department of Lymphoma/Myeloma, The University of Texas MD Anderson Cancer Center and lead investigator for the pivotal registration trial PCYC-1104. “With IMBRUVICA, we now have a once-daily oral therapy that has been shown to affect the disease. I’m proud to have been involved in this study.”

MCL is an orphan disease. Orphan diseases are characterized by high unmet need and small patient populations affecting fewer than 200,000 people.² In the U.S., approximately 2,900 new cases of MCL are diagnosed each year³ with a median age at diagnosis of 65.⁴ MCL typically involves the lymph nodes, but can spread to other tissues, such as the bone marrow, liver, spleen and gastrointestinal tract.⁵ This challenging disease is associated with poor prognoses.⁵

“The approval of IMBRUVICA is great news for MCL patients who have received prior therapy and the physicians who treat them,” said William Hait, M.D., Ph.D. global head, research and development, Janssen Research & Development, LLC. “The Breakthrough Therapy Designation helped turbo-charge our timelines – it’s a remarkable process. It’s an excellent example of collaboration between the FDA, Janssen and Pharmacylics.”

“Breakthrough Therapy Designation is intended to speed up the development and review of treatments to help address serious or life-threatening diseases. It is gratifying to see this early example of the new Breakthrough Therapy Designation pathway meeting its intention – getting promising treatments to patients who are waiting for new options,” said Dr. Ellen Sigal, chair and founder of Friends of Cancer Research, a think tank and advocacy organization based in Washington, DC.[†]

IMBRUVICA was granted three Breakthrough Therapy Designations by the FDA, including relapsed or refractory MCL. IMBRUVICA was approved under the FDA’s Subpart H regulation.⁶ Janssen and Pharmacylics are continuing an extensive clinical development program for IMBRUVICA, including Phase 3 study commitments in this patient population. Additionally, IMBRUVICA has been submitted to the FDA for the treatment of previously treated patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).

IMBRUVICA works by blocking a specific protein called Bruton’s tyrosine kinase (BTK).¹ Non-clinical studies have shown that blocking BTK inhibits malignant B-cell survival.¹

The safety and efficacy of IMBRUVICA in patients with MCL who have received at least one prior therapy were evaluated in an open-label, multi-center, single-arm Phase 2 study of 111 treated patients. The primary endpoint was investigator-assessed overall response rate (ORR). Based on investigator assessment, the ORR was 65.8 percent (95% CI 56.2, 74.5%) and the median duration of response was 17.5 months (95% CI 15.8, not reached).¹ This endpoint was based on responses assessed according to the revised International Working Group (IWG) for non-Hodgkin’s lymphoma (NHL) criteria.¹

The Warnings and Precautions for IMBRUVICA include hemorrhage, infections, myelosuppression, renal toxicity, second primary malignancies and embryo-fetal toxicity.

The most commonly occurring side effects (adverse reactions in 20 percent or more of patients in the clinical trial) were

thrombocytopenia*, diarrhea (51%), neutropenia*, anemia*, fatigue (41%), musculoskeletal pain (37%), peripheral edema (swelling of hands and feet, 35%), upper respiratory tract infection (34%), nausea (31%), bruising (30%), dyspnea (shortness of breath, 27%), constipation (25%), rash (25%), abdominal (stomach) pain (24%), vomiting (23%) and decreased appetite (21%). [**NOTE: Treatment-emergent decreases (all grades) of platelets (57%), neutrophils (47%) and hemoglobin (41%) were based on laboratory measurements and adverse reactions.*]

The most common Grade 3 or 4 non-hematological adverse reactions ($\geq 5\%$) were: pneumonia (7%), abdominal pain (5%), atrial fibrillation, diarrhea (5%), fatigue (5%), and skin infections (5%). Treatment-emergent Grade 3 or 4 cytopenias were reported in 41% of patients. Ten patients (9%) discontinued treatment due to adverse reactions in the trial (N=111).

The most frequent adverse reaction leading to treatment discontinuation was subdural hematoma (1.8%). Adverse reactions leading to dose reduction occurred in 14% of patients.

The recommended dose of IMBRUVICA is 560 mg (four 140 mg capsules) once daily.¹

The IMBRUVICA MCL study was published online in *The New England Journal of Medicine* in June 2013.⁷

Access to IMBRUVICA

IMBRUVICA is commercially available immediately. Janssen Biotech is striving to make the process of obtaining IMBRUVICA and navigating insurance benefits easy for patients by offering comprehensive access services and support for eligible patients. The YOU&i Access™ program is designed specifically for patients who are prescribed IMBRUVICA and provides personalized attention coupled with access services designed to make obtaining medication simple and convenient for patients and those involved in their care.

This includes a YOU&i Access™ Instant Savings program, which provides ePAY support and benefits information to eligible commercially-insured patients. Patients can access the program by contacting 1-877-877-3536, option 1 or by visiting www.IMBRUVICA.com.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage – Five percent (5%) of patients with MCL had Grade 3 or higher bleeding events (subdural hematoma, gastrointestinal bleeding, and hematuria). Bleeding events including bruising of any grade occurred in 48% of patients with MCL treated with 560 mg daily. The mechanism for the bleeding events is not well understood. Consider the benefit-risk of ibrutinib in patients requiring antiplatelet or anticoagulant therapies and the benefit-risk of withholding ibrutinib 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 have occurred. At least 25% of patients with MCL had infections \geq Grade 3, according to NCI Common Terminology Criteria for Adverse Events (CTCAE). Monitor patients for fever and infections and evaluate promptly.

Myelosuppression – Treatment-emergent Grade 3 or 4 cytopenias were reported in 41% of patients. These included neutropenia (29%), thrombocytopenia (17%) and anemia (9%). Monitor complete blood counts monthly.

Renal Toxicity – Fatal and serious cases of renal failure have occurred. Treatment-emergent increases in creatinine levels up to 1.5 times the upper limit of normal occurred in 67% of patients and from 1.5 to 3 times the upper limit of normal in 9% of patients. Periodically monitor creatinine levels. Maintain hydration.

Second Primary Malignancies – Other malignancies (5%) have occurred in patients with MCL who have been treated with IMBRUVICA, including skin cancers (4%), and other carcinomas (1%).

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. 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.

Adverse Reactions – The most commonly occurring adverse reactions ($\geq 20\%$) in the clinical trial were thrombocytopenia*, diarrhea (51%), neutropenia*, anemia*, fatigue (41%), musculoskeletal pain (37%), peripheral edema (35%), upper respiratory tract infection (34%), nausea (31%), bruising (30%), dyspnea (27%), constipation (25%), rash (25%), abdominal pain (24%), vomiting (23%) and decreased appetite (21%).

* Treatment-emergent decreases (all grades) of platelets (57%), neutrophils (47%) and hemoglobin (41%) were based on laboratory measurements and adverse reactions.

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Drug Interactions: CYP3A Inhibitors – Avoid concomitant administration with strong or moderate inhibitors of CYP3A. If a moderate CYP3A inhibitor must be used, reduce the IMBRUVICA dose.

CYP3A Inducers – Avoid co-administration with strong CYP3A inducers.

Special Populations – Hepatic Impairment – Avoid use in patients with baseline hepatic impairment.

For the full prescribing information, visit http://www.imbruvica.com/downloads/Prescribing_Information.pdf.

About IMBRUVICA

IMBRUVICA is indicated for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.¹ This indication is based on overall response rate (ORR). An improvement in survival or disease-related symptoms has not been established.¹

IMBRUVICA works by blocking a specific protein called Bruton's tyrosine kinase (BTK).¹ BTK is a signaling molecule of the B-cell antigen receptor (BCR) pathway, which is emerging as a target in some B-cell malignancies.^{8,9,10} BTK's role in signaling through the B-cell surface receptors results in activation of pathways necessary for B cell trafficking, chemotaxis and adhesion.¹

For more information, visit www.IMBRUVICA.com.

About Janssen Biotech, Inc.

Janssen Biotech, Inc. redefines the standard of care in immunology, oncology, urology and nephrology. Built upon a rich legacy of innovative firsts, Janssen Biotech has delivered on the promise of new treatments and ways to improve the health of individuals with serious disease. Beyond its innovative medicines, Janssen Biotech is at the forefront of developing education and public policy initiatives to ensure patients and their families, caregivers, advocates and health care professionals have access to the latest treatment information, support services and quality care. For more information on Janssen Biotech, Inc. or its products, visit www.janssenbiotech.com.

Janssen Biotech is one of the Janssen Pharmaceutical Companies of Johnson & Johnson, which are dedicated to addressing and solving some of the most important unmet medical needs in oncology, immunology, neuroscience, infectious diseases and vaccines, and cardiovascular and metabolic diseases. Driven by our commitment to patients, we work together to bring innovative ideas, products, services and solutions to people throughout the world. Follow us on Twitter at www.twitter.com/JanssenUS.

[†] *Janssen and Johnson & Johnson have provided funding to Friends of Cancer Research for educational and support initiatives benefiting cancer patients and their families.*

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¹ IMBRUVICA Prescribing Information, November 2013

² National Organization for Rare Disorders. "Rare Disease Information". Available from: <http://www.rarediseases.org/rare-disease-information/rare-disease-information>. Accessed September 2013.

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⁴ Humala K, Younes A. Current and emerging new treatment strategies for mantle cell lymphoma. *Leukemia & Lymphoma*. 2013; 54(5): 912–921.

⁵ Leukemia and Lymphoma Society. Mantle Cell Lymphoma Facts. Available from: <http://www.lls.org/content/nationalcontent/resourcecenter/freeeducationmaterials/lymphoma/pdf/mantlecelllymphoma.pdf>. Accessed August 2013.

⁶ The U.S. Food and Drug Administration. CFR - Code of Federal Regulations Title 21. Available from: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?CFRPart=314&showFR=1&subpartNode=21:5.0.1.1.4.8>. Accessed August 2013.

⁷ Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. *N Engl J Med* 2013 Jun 19 [epub ahead of print].

⁸ Buggy JJ and Elias L. Bruton tyrosine kinase (BTK) and its role in B-cell malignancy. *Int Rev Immunol*. 2012;31:119-132.

⁹ Woyach JA, Johnson AJ, and Byrd JC. The B-cell receptor signaling pathway as a therapeutic target in CLL. *Blood*. 2012;120(6):1175-1184

¹⁰ Davis RE, Ngo VN, Lenz G, et al. Chronic active B-cell receptor signaling in diffuse large B-cell lymphoma. *Nature*. 2010;463(7277):88-92