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U.S. Food and Drug Administration Approves IMBRUVICA™ (ibrutinib) as a Single Agent fo Patients with Chronic Lymphocytic Leukemia Who Have Received at Least One Prior Therapy

SUNNYVALE, Calif., Feb. 12, 2014 /PRNewswire/ -- Pharmacyclics, Inc. (NASDAQ: PCYC) today announced that the U.S. Food and Drug Administration (FDA) has approved IMBRUVICA™ (ibrutinib) as a single agent for the treatment of patients with chronic lymphocytic leukemia (CLL) 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 is the first once-daily, single-agent, oral kinase inhibitor for patients with CLL who have received one prior therapy[1] and is being jointly developed and commercialized by Pharmacyclics and Janssen Biotech, Inc.

"Rarely does a drug come along with so much potential to help CLL patients," said John C. Byrd, M.D., Director, Division of Hematology, The Ohio State University Comprehensive Cancer Center - Arthur G. James Cancer Hospital & Richard J. Solove Research Institute and lead investigator for the pivotal CLL trial PCYC-1102-CA. "I have been impressed with the promising and durable response rates we have seen in patients. It is particularly gratifying to see the difference that IMBRUVICA has made for patients in the clinical trials."

CLL is a slow-growing blood cancer of the white blood cells (lymphocytes), most commonly B-cells.[2] CLL is the most common adult leukemia.[3] Approximately 16,000 patients in the U.S. are diagnosed each year with CLL.[4] The prevalence of CLL is approximately 114,500 in the U.S.[5] CLL is a chronic disease that predominantly occurs in the elderly and the average age of diagnosis is 72.[2] Patients commonly receive multiple lines of treatment over the course of their disease.[2] Nearly 4,600 patients die of CLL every year[6] and the five-year survival is approximately 82 percent.[7]

IMBRUVICA was approved in CLL for patients who have received at least one prior therapy under the FDA's accelerated approval program. This second indication follows the approval of IMBRUVICA for patients with mantle cell lymphoma (MCL) after one prior therapy on November 13, 2013, granted under the agency's Breakthrough Therapy Designation.[1] Both indications are based on ORR.[1] An improvement in survival or disease-related symptoms has not been established. Most recently IMBRUVICA was included in the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Hodgkin's Lymphomas, Version 1.2014 for patients with relapsed/refractory (R/R) MCL and R/R CLL.[6] as a Category 2A recommendation.[8]

"Today's approval of IMBRUVICA is the first major milestone in the CLL clinical development plan, which includes seven Phase III trials, four of which are company sponsored, and covers all lines and various combinations of treatments," said Bob Duggan, CEO and Chairman of the Board of Pharmacyclics. "I would like to thank the patients and physicians for their trust and participation in our clinical trials. We are also thankful to the FDA for their collaboration and support, and a very big 'thank you' to the entire Pharmacyclics and Janssen teams who are tirelessly advancing our mission to serve for the betterment of patients."

IMBRUVICA inhibits the function of Bruton's tyrosine kinase (BTK).[1] BTK is a key signaling molecule of the B-cell receptor signaling complex that plays an important role in the survival and spread of malignant B-cells.[9, 10, 11] IMBRUVICA blocks signals that stimulate malignant B-cells to grow and divide uncontrollably.[1, 12]

The approval was based on the results of a Phase Ib/II, open-label, multi-center, international, single-arm trial of 48 patients with relapsed or refractory CLL who received 420mg of IMBRUVICA daily. The primary endpoint was safety and a secondary endpoint was ORR, which was assessed by a modified version of the International Working Group on CLL (IWCLL) criteria by an Independent Review Committee.[1] The efficacy results demonstrated a 58.3 percent ORR (95% confidence interval (CI) (%), 43.2, 72.4), all partial responses. The duration of response (DOR) ranged from 5.6 to 24.2+ months. The median DOR was not reached.

Safety was evaluated in the same 48 patients, with a median treatment duration of 15.6 months. The Warnings and Precautions listed in the Prescribing Information include hemorrhage, infections, myelosuppression, renal toxicity, second

primary malignancies and embryo-fetal toxicity.[1] The most commonly occurring adverse reactions (> 20%) in the clinical trial were (listed here as % all Grades, % Grade 3 or 4): thrombocytopenia (71%,10%), diarrhea (63%, 4%), bruising (54%,2%), neutropenia (54%,27%), anemia (44%,0%), upper respiratory tract infection (48%,26%), fatigue (31%,4%), musculoskeletal pain (27%,6%), rash (27%,0%), pyrexia (25%,2%), constipation (23%,2%), peripheral edema (23%,0%), arthralgia (23%,0%), nausea (21%,2%), stomatitis (21%,0%), sinusitis (21%,6%), and dizziness (21%, 0%).

Five patients (10%) discontinued treatment due to adverse reactions in the trial. These included three patients (6%) with infections and two patients (4%) with subdural hematomas. Adverse reactions leading to dose reduction occurred in thirteen percent of patients.[1] For additional safety information please see below for Important Safety Information and see the full Prescribing Information on the Company's website.

The recommended dose of IMBRUVICA in CLL is 420 mg (three 140 mg capsules) orally once daily.[1]

This approval of IMBRUVICA in CLL triggers a $60 million milestone payment to Pharmacyclics under its collaboration agreement with Janssen Biotech Inc.

Corporate Conference Call
The Company will hold a conference call today at 2:30 p.m. ET to discuss these events. To participate in the conference call, please dial 1-877-303-7908 for domestic callers and 1-678-373-0875 for international callers. To access the live audio broadcast or the subsequent archived recording, log on to http://ir.pharmacyclics.com/events.cfm. To access a replay of the call please dial 1-855-859-2056 for domestic callers and 1-404-537-3406 for international callers and use the conference ID number: 96901967. The archived version of the webcast and conference call will be available for 30 days on the Investor Relations section of the Company's Web site at http://www.pharmacyclics.com.

INDICATIONS
IMBRUVICA™ (ibrutinib) is indicated for the treatment of:

- Patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.
- Patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy.

These indications are based on overall response rate. Improvements in survival or disease-related symptoms have not been established.

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS
Hemorrhage -
Five percent of patients with MCL and 6% of patients with CLL had Grade 3 or higher bleeding events (subdural hematoma, ecchymoses, gastrointestinal bleeding, and hematuria). Overall, bleeding events including bruising of any grade occurred in 48% of patients with MCL treated with 560 mg daily and 63% of patients with CLL treated at 420 mg daily.

The mechanism for the bleeding events is not well understood. IMBRUVICA™ may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies. 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 have occurred with IMBRUVICA™ therapy. At least 25% of patients with MCL and 35% of patients with CLL had infections Grade 3 or greater 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 with MCL and 35% of patients with CLL. These included neutropenia (29%), thrombocytopenia (17%) and anemia (9%) in patients with MCL and neutropenia (27%) and thrombocytopenia (10%) in patients with CLL. Monitor complete blood counts monthly.

Renal Toxicity - Fatal and serious cases of renal failure have occurred with IMBRUVICA™ therapy. Treatment-emergent increases in creatinine levels up to 1.5 times the upper limit of normal occurred in 67% of patients with MCL and 23% of patients with CLL. Increases in creatinine 1.5 to 3 times the upper limit of normal occurred in 9% of patients with MCL and 4% of patients with CLL. Periodically monitor creatinine levels. Maintain hydration.

Second Primary Malignancies - Other malignancies have occurred in 5% of patients with MCL and 10% of patients with CLL who have been treated with IMBRUVICA™. Four percent of patients with MCL, had skin cancers, and 1% had other carcinomas. Eight percent of patients with CLL had skin cancers and 2% had other carcinomas.

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 -
MCL: The most commonly occurring adverse reactions (≥ 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.

The most common Grade 3 or 4 non-hematological adverse reactions (≥ 5%) were pneumonia (7%), abdominal pain (5%), atrial fibrillation (5.4%), 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.

CLL: The most commonly occurring adverse reactions (≥ 20%) in the clinical trial were thrombocytopenia*, diarrhea (63%), bruising (54%), neutropenia*, anemia*, upper respiratory tract infection (48%), fatigue (31%), musculoskeletal pain (27%), rash (27%), pyrexia (25%), constipation (23%), peripheral edema (23%), arthralgia (23%), nausea (21%), stomatitis (21%), sinusitis (21%), and dizziness (21%).

*Treatment-emergent decreases (all grades) of platelets (71%), neutrophils (54%) and hemoglobin (44%) were based on laboratory measurements per IWCLL criteria and adverse reactions.

The most common Grade 3 or 4 non-hematological adverse reactions (≥ 5%) were pneumonia (8%), hypertension (8%), atrial fibrillation (6.3%), sinusitis (6%), skin infection (6%), dehydration (6.4%), and musculoskeletal pain (6%). Treatment-emergent Grade 3 or 4 cytopenias were reported in 35% of patients.

Five patients (10%) discontinued treatment due to adverse reactions in the trial (N=48). These included 3 patients (6%) with infections and 2 patients (4%) with subdural hematomas. Adverse reactions leading to dose reduction occurred in 13% of patients.

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

Access to IMBRUVICA
Patients who are prescribed IMBRUVICA can receive access support through several distinct programs:

- The YOU&i Start™ program enables eligible patients who have been prescribed IMBRUVICA for an FDA-approved indication and are experiencing insurance coverage delays to access free product for a limited period of time, if they meet certain requirements. In addition, our YOU&i Access service center is set up to help patients ensure that all access-related administration is properly handled.
- The YOU&i Access™ Instant Savings Program helps commercially insured patients who have difficulties with out-of-pocket expenses for IMBRUVICA. Eligible patients may receive support to reduce their monthly out-of-pocket costs to $25.
- Patients who are deemed uninsured and eligible, and who qualify based on financial need, can access IMBRUVICA through the Johnson & Johnson Patient Assistance Foundation (JJPAF), an independent non-profit organization to which Pharmacyclics makes donations.
- Pharmacyclics will also support third party foundations, organizations and other efforts to help patients in need get access to appropriate care.

More information about these comprehensive patient access programs is accessible at 1-877-877-3536 or at www.IMBRUVICA.com.

About IMBRUVICA
IMBRUVICA is indicated for the treatment of patients with mantle cell lymphoma or chronic lymphocytic leukemia who have received at least one prior therapy.[1] For more information about IMBRUVICA, including the full prescribing information, please visit www.IMBRUVICA.com. IMBRUVICA is a first in class, oral therapy and is a new agent that inhibits a protein called Bruton's tyrosine kinase (BTK).[1] BTK is a key signaling molecule of the B-cell receptor signaling complex that plays an important role in the survival and spread of malignant B-cells.[8,9,10] IMBRUVICA blocks signals that tell malignant B-cells to multiply and spread uncontrollably.[1,11] It is one of the first medicines to file for FDA approval via the new Breakthrough Therapy Designation pathway, enabling Pharmacyclics to rapidly bring this medicine to patients in need.

To date, ten Phase III trials have been initiated with ibrutinib and a total of 41 trials are currently registered on www.clinicaltrials.gov. Janssen and Pharmacyclics entered a collaboration and license agreement in December 2011 to co-develop and co-commercialize IMBRUVICA.

About Pharmacyclics
Pharmacyclics® is a biopharmaceutical company focused on developing and commercializing innovative small-molecule drugs for the treatment of cancer and immune mediated diseases. Our mission and goal is to build a viable biopharmaceutical company that designs, develops and commercializes novel therapies intended to improve quality of life, increase duration of life and resolve serious unmet medical healthcare needs; and to identify and control promising product candidates based on scientific development and administrational expertise, develop our products in a rapid, cost-efficient manner and pursue commercialization and/or development partners when and where appropriate.

Pharmacyclics markets IMBRUVICA and has three product candidates in clinical development and several preclinical molecules in lead optimization. The company is committed to high standards of ethics, scientific rigor, and operational efficiency as it moves each of these programs to viable commercialization.

Pharmacyclics is headquartered in Sunnyvale, California and is listed on NASDAQ under the symbol PCYC. To learn more about how Pharmacyclics advances science to improve human healthcare visit us at www.pharmacyclics.com.

NOTE: This announcement may contain forward-looking statements made in reliance upon the safe harbor provisions of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, including statements, among others, relating to our future capital requirements, including our expected liquidity position and timing of the receipt of certain milestone payments, and the sufficiency of our current assets to meet these requirements, our future results of operations, our expectations for and timing of ongoing or future clinical trials and regulatory approvals for any of our product candidates, and our plans, objectives, expectations and intentions. Because these statements apply to future events, they are subject to risks and uncertainties. When used in this announcement, the words "anticipate", "believe", "estimate", "expect", "expectation", "goal", "should", "would", "project", "plan", "predict", "intend", "target" and similar expressions are intended to identify such forward-looking statements. These forward-looking statements are based on information currently available to us and are subject to a number of risks, uncertainties and other factors that could cause our actual results, performance, expected liquidity or achievements to differ materially from those projected in, or implied by, these forward-looking statements. Factors that may cause such a difference include, without limitation, our need for substantial additional financing and the availability and terms of any such financing, the safety and/or efficacy results of clinical trials of our product candidates, our failure to obtain regulatory approvals or comply with ongoing governmental regulation, our ability to commercialize, manufacture and achieve market acceptance of any of our product candidates, for which we rely heavily on collaboration with third parties, and our ability to protect and enforce our intellectual property rights and to operate without infringing upon the proprietary rights of third parties. Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee future results, performance or achievements and no assurance can be given that the actual results will be consistent with these forward-looking statements. For more information about the risks and uncertainties that may affect our results, please see the Risk Factors section of our filings with the Securities and Exchange Commission, including our transition report on Form 10-K for the six month period ended *December 31, 2012* and quarterly reports on Form 10-Q. We do not intend to update any of the forward-looking statements after the date of this announcement to conform these statements to actual results, to changes in management's expectations or otherwise, except as may be required by law.

Contacts:

Media
Manisha Pai
Senior Director, Public Relations and Corporate Communications
Phone: 408-215-3720
Cell: 617-510-9193

Investors
Ramses Erdtmann
Senior Vice President, Investor Relations
Phone: 408-215-3325

U.S. Medical Information, Pharmacyclics
877-877-3536

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[5] IMS [Data on file] IMS patient claims estimates for July 2012-June 2013. Note: This information is an estimate derived from the use of information under license from the following IMS Health Incorporated information service: IMS Oncology Tracking Reports for the period July 2012 to June 2013. IMS expressly reserves all rights, including rights of copying, distribution and republication. *Pharmacyclics, Inc. makes no representation with respect to the accuracy or reliability of this information. Investors are advised to independently verify this information before using it to make investment decisions.*
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Dr. John Byrd serves as national principal investigator of this Pharmacyclics-sponsored clinical study forming the basis for ibrutinib FDA-approval. He has served as an unpaid advisor to both Pharmacyclics and Janssen in developing the compound ibrutinib. Dr. Byrd does not have a financial interest in either company.

SOURCE Pharmacyclics