U.S. FDA Expands IMBRUVICA® (ibrutinib) Label to Include Overall Survival Data in Previously Untreated Chronic Lymphocytic Leukemia (CLL), New Indication for Small Lymphocytic Lymphoma (SLL) Patients and Combination Dosing IMBRUVICA® with Bendamustine and Rituximab (BR) for CLL/SLL patients.

Update to the IMBRUVICA® U.S. Prescribing Information includes overall survival data from RESONATE-2 study showing significant improvements in previously untreated CLL/SLL patients with IMBRUVICA® compared to chemotherapy (chlorambucil). The label update also includes data from the HELIOS trial providing first-ever IMBRUVICA® data in combination with bendamustine and rituximab in relapsed/refractory CLL/SLL patients.

The IMBRUVICA® label has been updated with safety and efficacy data from the Phase 3 HELIOS (CLL3001) trial assessing the use of IMBRUVICA® in combination with bendamustine and rituximab (BR) versus placebo plus BR in relapsed/refractory patients with CLL/SLL. Following a review of the November 2015 supplemental New Drug Application (sNDA), the FDA has approved a new IMBRUVICA® indication to include the treatment of patients with SLL with or without the deletion of chromosome 17p (del 17p). IMBRUVICA® is jointly developed and commercialized by Pharmacyclics LLC, an AbbVie Company, and Janssen Biotech, Inc.

The RESONATE-2 trial served as the basis for the March 2016 FDA approval of IMBRUVICA® for the first-line treatment of CLL patients. Notably, the OS data now included in the IMBRUVICA® PI provides a longer-term update to results published in *The New England Journal of Medicine,* with a median follow-up of 28.1 months. The label updates based on HELIOS represent the first-ever data demonstrating an improvement in progression-free survival (PFS) and overall response rate (ORR) with IMBRUVICA® when combined with BR versus placebo plus BR in patients with relapsed/refractory CLL/SLL.

The National Comprehensive Cancer Network (NCCN) published an update to its clinical practice guidelines for non-Hodgkin's lymphomas, granting IMBRUVICA® a category 1 recommendation for certain CLL patients, the highest recommendation assigned by the organization. Specifically, NCCN recommends IMBRUVICA® as a first-line treatment option for frail CLL patients with significant comorbidities, as well as for CLL patients with or without del 17p or the genetic mutation TP53 who are 70 years or older, or younger patients with significant comorbidities. The NCCN guidelines inform prescribing and reimbursement practices in many institutions in the U.S. and internationally.

IMBRUVICA® Safety in CLL/SLL

Warnings and Precautions include hemorrhage, infections, cytopenias, atrial fibrillation, hypertension, second primary malignancies, tumor lysis syndrome and embryo-fetal toxicity.

Four to 10% of patients receiving IMBRUVICA® in the studies supporting the CLL indications (PCYC-1102, RESONATE™ [PCYC-1112], RESONATE-2 [PCYC-1115] and HELIOS [CLL3001]) discontinued treatment due to adverse reactions (ARs). These included pneumonia, hemorrhage, atrial fibrillation, rash and neutropenia (1% each). ARs leading to dose reduction occurred in approximately 6% of patients.

The ARs from the RESONATE-2 trial reported in the IMBRUVICA® U.S. PI reflect exposure to IMBRUVICA® with a median duration of 17.4 months versus a median exposure to chlorambucil of 7.1 months. The most common ARs (≥20%) of any Grade in the RESONATE-2 trial for IMBRUVICA® were diarrhea (42%),

musculoskeletal pain* (36%), cough (22%) and rash* (21%). The most common Grade 3/4 AR (>5%) was pneumonia* (8%).

The ARs from the HELIOS trial reported in the IMBRUVICA® U.S. PI reflect exposure to IMBRUVICA® + BR with a median duration of 14.7 months versus a median exposure to placebo + BR of 12.8 months. The most common ARs (≥20%) of any Grade in the HELIOS trial for IMBRUVICA® plus BR were neutropenia* (66%), diarrhea (36%), thrombocytopenia* (34%), rash* (32%), musculoskeletal pain* (29%), pyrexia (25%) and bruising* (20%). The most common Grade 3/4 ARs (≥5%) were neutropenia* (61%), thrombocytopenia* (16%) and hypertension* (5%).

**Includes multiple ADR terms*

CLL/SLL INDICATIONS:

IMBRUVICA® is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). IMBRUVICA® is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL)/small lymphocytic leukemia (SLL) with 17p deletion.

CLL/SLL DOSAGE:

The recommended dose of IMBRUVICA® for CLL/SLL and WM is 420 mg (three 140 mg capsules) orally once daily until disease progression or unacceptable toxicity.

The recommended dose of IMBRUVICA® for CLL/SLL when used in combination with bendamustine and rituximab (administered every 28 days for up to 6 cycles) is 420 mg (three 140 mg capsules) orally once daily until disease progression or unacceptable toxicity.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage - Fatal bleeding events have occurred in patients treated with IMBRUVICA®. Grade 3 or higher bleeding events (intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post-procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with IMBRUVICA®. The mechanism for the bleeding events is not well understood. IMBRUVICA® may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding. Consider the benefit-risk of withholding IMBRUVICA® for at least 3 to 7 days pre- and postsurgery depending upon the type of surgery and the risk of bleeding.

Infections - Fatal and nonfatal infections have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 14% to 29% of patients. Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with IMBRUVICA®. Evaluate patients for fever and infections and treat appropriately.

Cytopenias - Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 19% to 29%), thrombocytopenia (range, 5% to 17%), and anemia (range, 0% to 9%) based on laboratory measurements occurred in patients treated with single agent IMBRUVICA®. Monitor complete blood counts monthly.

Atrial Fibrillation - Atrial fibrillation and atrial flutter (range, 6% to 9%) have occurred in patients treated with IMBRUVICA®, particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. Patients

who develop arrhythmic symptoms (eg, palpitations, lightheadedness) or new-onset dyspnea should have an ECG performed. Atrial fibrillation should be managed appropriately and if it persists, consider the risks and benefits of IMBRUVICA® treatment and follow dose modification guidelines.

Hypertension - Hypertension (range, 6% to 17%) has occurred in patients treated with IMBRUVICA® with a median time to onset of 4.6 months (range, 0.03 to 22 months). Monitor patients for new-onset hypertension or hypertension that is not adequately controlled after starting IMBRUVICA®. Adjust existing antihypertensive medications and/or initiate antihypertensive treatment as appropriate.

Second Primary Malignancies - Other malignancies (range, 5% to 16%) including non-skin carcinomas (range, 1% to 4%) have occurred in patients treated with IMBRUVICA®. The most frequent second primary malignancy was non-melanoma skin cancer (range, 4% to 13%).

Tumor Lysis Syndrome - Tumor lysis syndrome has been infrequently reported with IMBRUVICA® therapy. Assess the baseline risk (eg, 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.

ADVERSE REACTIONS

The most common adverse reactions (≥20%) in patients with B-cell malignancies (MCL, CLL/SLL, and WM) were neutropenia* (64%), thrombocytopenia* (63%), diarrhea (43%), anemia*(41%), musculoskeletal pain (30%), rash (29%), nausea (29%), bruising (29%), fatigue (27%), hemorrhage (21%), and pyrexia 21%).

*Based on adverse reactions and/or laboratory measurements (noted as platelets, neutrophils, or hemoglobin decreased).

The most common Grade 3 or 4 non-hematologic adverse reactions (≥5%) in MCL patients were pneumonia (7%), abdominal pain (5%), atrial fibrillation (5%), diarrhea (5%), fatigue (5%), and skin infections (5%). Approximately 6% (CLL), 14% (MCL), and 11% (WM) of patients had a dose reduction due to adverse reactions.

Approximately 4%-10% (CLL), 9% (MCL), and 6% (WM) of patients discontinued due to adverse reactions. Most frequent adverse reactions leading to discontinuation were pneumonia, hemorrhage, atrial fibrillation, rash and neutropenia (1% each) in CLL patients and subdural hematoma (1.8%) in MCL patients.

DRUG INTERACTIONS

CYP3A Inhibitors - Avoid coadministration with strong and moderate CYP3A inhibitors. If a moderate CYP3A inhibitor must be used, reduce the IMBRUVICA® dose.

CYP3A Inducers - Avoid coadministration with strong CYP3A inducers.

SPECIFIC POPULATIONS

Hepatic Impairment - Avoid use in patients with moderate or severe baseline hepatic impairment. In patients with mild impairment, reduce IMBRUVICA® dose.

Please see Full Prescribing
Information: http://www.imbruvica.com/downloads/Prescribing_Information.pdf.