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RUVICA (ibrutinib) capsules approved for treatment-naïve CLL patients

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The U.S. Food and Drug Administration (FDA) has approved IMBRUVICA® (ibrutinib) capsules for treatment-naïve patients with chronic lymphocytic leukemia (CLL). The approval is based on data from the Phase 3 RESONATE-2 (PCYC-1115) study, the first head-to-head clinical trial comparing IMBRUVICA to a chemotherapy agent. Results showed IMBRUVICA significantly extended progression-free survival (PFS; the primary endpoint) and increased overall response rate (ORR; a key secondary endpoint) compared to chlorambucil in previously untreated patients with CLL age 65 or older. IMBRUVICA is now approved for use in all lines of CLL therapy, considerably expanding the number of patients who may benefit from this treatment. This broadens the indication beyond the initial CLL approval in February 2014 for the treatment of patients with CLL who have received at least one prior therapy and in July 2014 for CLL patients with del 17p, a genetic mutation typically associated with poor treatment outcomes. IMBRUVICA is jointly developed and commercialized by Janssen Biotech, Inc. and Pharmacyclics LLC, an AbbVie company.

On a related front, the National Comprehensive Cancer Network® (NCCN) published an update on February 17 to its Clinical Practice Guidelines for non-Hodgkin's lymphomas recommending IMBRUVICA for certain first-line CLL patients.

"People living with CLL who have not been previously treated now have an option that significantly improved progression-free survival when compared to the oral chemotherapy used in the RESONATE-2 trial," said Jan Burger, M.D., Ph.D., Associate Professor, Department of Leukemia, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX and RESONATE-2 study lead investigator. "The results seen in the RESONATE-2 clinical trial are truly compelling and make this medicine an attractive first-line treatment option for clinicians in the hematology space."

The expanded IMBRUVICA indication is based on data from the Phase 3, randomized, open-label RESONATE-2 trial, which showed IMBRUVICA significantly improved PFS and ORR versus chlorambucil in treatment-naïve patients aged 65 or older with CLL or small lymphocytic lymphoma (SLL). The PFS as assessed by an Independent Review Committee (IRC) according to the clarified International Workshop on Chronic Lymphocytic Leukemia (iWCLL) criteria indicated an 84 percent statistically significant reduction in the risk of death or progression in the IMBRUVICA arm versus the chlorambucil arm (HR=0.161 [95 percent CI, 0.091-0.283]). Median PFS was not reached for IMBRUVICA versus 18.9 months for chlorambucil (95 percent CI: 14.1, 22.0). Data from RESONATE-2 were presented in an oral session at the American Society of Hematology (ASH) Annual Meeting on December 7, 2015, in addition to being featured in the official ASH press program and simultaneously published online in *The New England Journal of Medicine*.

CLL is a slow-growing blood cancer that most commonly arises from B cells, a type of white blood cell (lymphocyte) that originates in the bone marrow. CLL is predominantly a disease of the elderly, with a median age of 71 at diagnosis.

"The IMBRUVICA story gets better and better. The results of RESONATE-2 demonstrate how IMBRUVICA can change the treatment strategies for many patients with CLL in the treatment-naïve setting. We anticipate this approval will give clinicians and more of their patients the opportunity to explore the efficacy and safety of treatment with IMBRUVICA for this disease," said Peter F. Lebowitz, M.D., Ph.D., Global Oncology Head, Janssen Research & Development, LLC.

Janssen and Pharmacyclics continue to support an extensive clinical development program for IMBRUVICA, including 16 Phase 3 study commitments in multiple patient populations.

IMBRUVICA in First-line, Elderly CLL Patients
The safety and efficacy of IMBRUVICA were evaluated in the randomized, international, multi-center, open-label Phase 3 RESONATE-2 trial in 269 treatment-naïve patients with CLL/SLL aged 65 years or older. Patients were randomized to receive either IMBRUVICA 420 mg orally, once daily until progression or unacceptable toxicity or chlorambucil 0.5 to 0.8 mg/kg on days 1 and 15 of each 28-day cycle for up to 12 cycles, with an allowance for

intrapatient dose increases up to 0.8mg/kg based on tolerability.

The primary endpoint of the study was met, with IMBRUVICA demonstrating a longer PFS versus chlorambucil as determined by the IRC per clarified iWCLL criteria. The hazard ratio was 0.161 (95 percent CI, 0.091-0.283, P<0.0001), which represents a reduction of risk of progression or death by 84 percent versus chlorambucil (median PFS not reached for IMBRUVICA vs. 18.9 months for chlorambucil [95 percent CI: 14.1, 22.0]); IMBRUVICA was associated with a significantly higher ORR (a composite of complete and partial responses [82.4 percent vs. 35.3 percent; P<0.0001]) as assessed by the IRC per modified iWCLL criteria. Notably, five patients (3.7 percent) in the IMBRUVICA arm and two patients (1.5 percent) in the chlorambucil arm achieved a complete response.

The safety of IMBRUVICA in this patient population was consistent with previously reported studies. The adverse reactions (AR) reported in the U.S. Prescribing Information reflect exposure to IMBRUVICA with a median duration of 17.4 months versus a median exposure to chlorambucil of 7.1 months: nearly 2.5 times longer exposure for IMBRUVICA. Warnings and Precautions include hemorrhage, infections, cytopenias, atrial fibrillation, hypertension, second primary malignancies, tumor lysis syndrome and embryo-fetal toxicity. The most common ARs (≥20 percent) of any Grade in the RESONATE-2 trial for IMBRUVICA were diarrhea (42 percent), musculoskeletal pain (36 percent), cough (22 percent) and rash (21 percent). The most common Grade 3/4 AR (>five percent) was pneumonia (eight percent). Four to 10 percent of patients receiving IMBRUVICA in the studies supporting the CLL indications (PCYC-1102, RESONATE [PCYC-1112] and RESONATE-2) discontinued treatment due to ARs. These included pneumonia, subdural hematomas and atrial fibrillation (one percent each). ARs leading to dose reduction occurred in approximately four percent of patients.

Source:
Janssen Biotech, Inc.