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AbbVie Announces Fourth Breakthrough Therapy Designation Granted by the U.S. Food and Drug Administration (FDA) for Ibrutinib (IMBRUVICA®) for Chronic Graft-Versus-Host-Disease (cGVHD), a Rare Condition with Limited Treatment Options

- FDA also granted ibrutinib Orphan Drug Designation for this condition. There are currently no therapies specifically approved for cGVHD, a severe and potentially life-threatening condition in which transplanted cells from donor attack the patient's body
- This latest milestone also highlights the potential benefit of ibrutinib's unique mechanism of action beyond oncology

NORTH CHICAGO, Ill., June 29, 2016 /PRNewswire/ -- AbbVie (NYSE: ABBV), a global biopharmaceutical company, today announced that the U.S. Food and Drug Administration (FDA) granted a fourth Breakthrough Therapy Designation (BTD) for ibrutinib (IMBRUVICA®) as a potential treatment of chronic graft-versus-host-disease (cGVHD) after failure of one or more lines of systemic therapy. The FDA also granted the therapy Orphan Drug Designation (ODD) for the condition. cGVHD is a severe and potentially life-threatening condition in which transplanted cells from the donor attack the patient's body.[1] Patients may develop this common complication after undergoing allogeneic stem cell or bone marrow transplantation in which they receive cells from a donor.[1] There are currently no therapies specifically approved for this condition. Most patients with cGVHD are prescribed glucocorticoids, a systemic steroid treatment that is able to act upon cells throughout the entire body;[2] however, research shows that long-term use of steroids can lead to serious health complications.[3]

The request for a BTD for ibrutinib in patients with cGVHD was based on preliminary clinical data from a Phase 1b/2 study evaluating the safety and efficacy of ibrutinib for the treatment of patients with steroid-dependent or refractory cGVHD. Overall, ibrutinib has shown compelling preclinical data, a novel mechanism of action and promising early clinical efficacy data supporting an improvement in cGVHD based on the National Institutes of Health (NIH) consensus cGVHD Activity Assessment. Preliminary results from this trial were previously presented at the 42nd Annual Meeting of the European Society for Blood and Marrow Transplantation (ESBM) in April 2016 and the 51st American Society of Clinical Oncology (ASCO) Annual Meeting in May 2015.

According to the FDA, a BTD is intended to expedite the development and review of a potential new drug for serious or life-threatening diseases where "preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development."[4] Similarly, ODD provides special status to a therapy developed to treat a rare condition or disease.[5]

"This fourth Breakthrough Therapy Designation from the FDA shows the promise of IMBRUVICA and its unique mechanism of action as a potential therapy beyond blood cancers, including chronic graft-versus-host-disease, a severe inflammatory condition with currently no approved therapies specifically for these patients," said Danelle James, M.D., M.S., Head of Oncology at Pharmacyclics. "We are committed to continuing to evaluate the potential benefit ibrutinib may offer in treating blood cancers, solid tumors and other health conditions with unmet medical needs."

In February 2013 (http://www.pharmacyclics.com/docs/librariesprovider4/press-release-archive/2013/pharmacyclics-first-to-announce-breakthrough-therapy-designation-in-oncology-from-the-u-s-food-and-drug-administration.pdf?sfvrsn=4) , the FDA granted BTD to IMBRUVICA for the treatment of patients with relapsed or refractory mantle cell lymphoma (MCL) and for the treatment of patients with Waldenström's macroglobulinemia (WM). In April 2013 (http://www.pharmacyclics.com/docs/librariesprovider4/press-release-archive/2013/pharmacyclics-announces-third-breakthrough-therapy-designation-for-ibrutinib-from-the-u-s-food-and-drug-administration.pdf?sfvrsn=4) , IMBRUVICA was awarded a third BTD for the treatment of patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) with a deletion of the short arm of chromosome 17 (del 17p). The Administration also assigned IMBRUVICA ODD for all three indications.

IMBRUVICA is jointly developed and commercialized by Pharmacyclics LLC, an AbbVie company and Janssen Biotech, Inc.

About IMBRUVICA

IMBRUVICA is a first-in-class, oral, once-daily therapy that inhibits a protein called Bruton's tyrosine kinase (BTK). BTK is a key signaling molecule in the B-cell receptor signaling complex that plays an important role in the survival and spread of malignant B cells.[6,7] IMBRUVICA blocks signals that tell malignant B cells to multiply and spread uncontrollably.[6]

IMBRUVICA is approved to treat patients with CLL/SLL including patients with 17p deletion, patients with MCL who have received at least one prior therapy and patients with WM. Accelerated approval was granted for the MCL indication based on overall response rate. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.[6]

IMBRUVICA was one of the first medicines to receive U.S. FDA approval via the new Breakthrough Therapy Designation pathway.

IMBRUVICA is being studied alone and in combination with other treatments in several blood and solid tumor cancers and other serious illnesses. More than 6,000 patients have been treated with IMBRUVICA in clinical trials. Currently, 14 Phase 3 trials have been initiated with IMBRUVICA and more than 90 trials are registered on www.clinicaltrials.gov (http://www.clinicaltrials.gov/) .

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:
https://www.imbruvica.com/docs/librariesprovider7/default-document-library/prescribing_information.pdf.

About AbbVie

AbbVie is a global, research-based biopharmaceutical company formed in 2013 following separation from Abbott Laboratories. The company's mission is to use its expertise, dedicated people and unique approach to innovation to develop and market advanced therapies that address some of the world's most complex and serious diseases. Together with its wholly-owned subsidiary, Pharmacyclics, AbbVie employs more than 28,000 people worldwide and markets medicines in more than 170 countries. For further information on the company and its people, portfolio and commitments, please visit www.abbvie.com (http://www.abbvie.com/) . Follow @abbvie (http://twitter.com/abbvie) on Twitter or view careers on our Facebook (http://www.facebook.com/abbviecareers) or LinkedIn (http://www.linkedin.com/company/abbvie) page.

Forward-Looking Statements

Some statements in this news release may be forward-looking statements for purposes of the Private Securities Litigation Reform Act of 1995. The words "believe," "expect," "anticipate," "project" and similar expressions, among others, generally identify forward-looking statements. AbbVie cautions that these forward-looking statements are subject to risks and uncertainties that may cause actual results to differ materially from those indicated in the forward-looking statements. Such risks and uncertainties include, but are not limited to, challenges to intellectual property, competition from other products, difficulties inherent in the research and development process, adverse litigation or government action, and changes to laws and regulations applicable to our industry. Additional information about the economic, competitive, governmental, technological and other factors that may affect AbbVie's operations is set forth in Item 1A, "Risk Factors," in AbbVie's 2015 Annual Report on Form 10-K, which has been filed with the Securities and Exchange Commission. AbbVie undertakes

no obligation to release publicly any revisions to forward-looking statements as a result of subsequent events or developments, except as required by law.

IMBRUVICA is a registered trademark of Pharmacyclics LLC

[1] MedlinePlus, U.S. National Library of Medicine. Graft-versus-host-disease. Available from: http://www.nlm.nih.gov/medlineplus/ency/article/001309.htm (http://www.nlm.nih.gov/medlineplus/ency/article/001309.htm) . Accessed March 2016.

[2] National Cancer Institute. NCI Dictionary of Cancer Terms. Available from: http://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45922 (http://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45922) . Accessed June 2016.

[3] Fred Hutchinson Cancer Research Center, Graft-vs.-Host-Disease. Available from: https://www.fredhutch.org/en/treatment/long-term-follow-up/FAQs/gvhd.html#2. Accessed June 2016.

[4] U.S. Food and Drug Administration, Fact Sheet: Breakthrough Therapies. Available from: http://www.fda.gov/RegulatoryInformation/Legislation/SignificantAmendmentstotheFDCAct/FDASIA/ucm329491.htm (http://www.fda.gov/RegulatoryInformation/Legislation/SignificantAmendmentstotheFDCAct/FDASIA/ucm329491.htm) . Accessed June 2016.

[5] U.S. Food and Drug Administration. Developing Products for Rare Diseases & Conditions. Available from: http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/ucm2005525.htm (http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/ucm2005525.htm) . Accessed June 2016.

[6] IMBRUVICA US Prescribing Information, May 2016.

[7] Genetics Home Reference. Isolated growth hormone deficiency. Available from: http://ghr.nlm.nih.gov/condition/isolated-growth-hormone-deficiency (http://ghr.nlm.nih.gov/condition/isolated-growth-hormone-deficiency) . Accessed May 2016.

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