Bristol-Myers Squibb and AbbVie Announce European Commission Approval of Empliciti™ (elotuzumab) for the Treatment of Multiple Myeloma in Adult Patients Who Have Received at Least One Prior Therapy

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Dateline City: PRINCETON, N.J.

First and only immunostimulatory antibody approved in the European Union for multiple myeloma

Accelerated assessment and approval based on long-term data from ELOQUENT-2, which evaluated Empliciti in combination with Revlimid® (lenalidomide) and dexamethasone (Rd)

ELOQUENT-2 demonstrated the Empliciti combination delivered a 53% relative improvement in progression-free survival vs. Rd alone at three years (23% vs. 15%)

PRINCETON, N.J. - (BUSINESS WIRE) -- Bristol-Myers Squibb Company (NYSE:BMY) and AbbVie (NYSE:ABBV) announced today that the European Commission has approved Empliciti™ (elotuzumab) for the treatment of multiple myeloma as combination therapy with Revlimid® (lenalidomide) and dexamethasone in patients who have received at least one prior therapy. Empliciti is now the first and only immunostimulatory antibody approved for multiple myeloma in the European Union (EU).

The approval is based on data from the randomized, open-label, Phase 3 ELOQUENT-2 study, which evaluated Empliciti in combination with lenalidomide and dexamethasone (ERd) versus lenalidomide and dexamethasone (Rd) alone. The co-primary endpoints of this study, progression-free survival (PFS) as assessed by hazard ratio (HR) and overall response rate (ORR), were achieved, with extended follow-up data showing a 53% relative improvement in PFS rate at three years (23% versus 15%). Additionally, a pre-specified interim analysis for overall survival (OS) found a positive trend favoring the Empliciti combination versus Rd alone (HR=0.77 [95% CI: 0.61, 0.97, \(p=0.0257\)]), though at the time of the interim analysis, the OS endpoint had not reached the pre-determined threshold for statistical significance. Patients will continue to be followed for survival, and the final analysis is pending. Empliciti with lenalidomide and dexamethasone is associated with the following Warnings and Precautions: infusion reactions, infections, second primary malignancies, hepatotoxicity, interference with determination of complete response, pregnancy/females and males of reproductive potential, and adverse reactions. Please see detailed Important Safety Information below.

“At Bristol-Myers Squibb, we are committed to delivering pioneering medicines with the goal of revolutionizing the way cancer is treated for patients who inspire our work each and every day,” said Emmanuel Blin, senior vice president and head of Commercialization, Policy and Operations, Bristol-Myers Squibb. “With the approval of Empliciti in the EU, we are proud to extend our Immuno-Oncology science to multiple myeloma patients in Europe who have received at least one prior therapy.”

In ELOQUENT-2, Empliciti was evaluated in patients who had received one to three prior therapies. The study demonstrated that the ERd regimen resulted in a 32% reduction in the risk of disease progression or death compared to Rd alone (HR=0.68 [97.61% CI: 0.55, 0.85, \(p=0.0001\)]). The ERd regimen also showed a 21% relative improvement in PFS rate at one year (68% versus 56%) and a 50% relative improvement in PFS rate at two years (39% versus 26%) compared to Rd alone. The ERd regimen demonstrated a significant improvement in ORR of 78.5% (95% Cl: 73.6-82.9; \(p=0.0002\)) versus 65.5% in the Rd arm (95% Cl: 60.1-70.7). The extended follow-up analysis also showed ERd had a median delay of one year in the time to next treatment compared to Rd alone: 33.35 months (95% Cl: 26.15, 40.21) versus 21.22 months (95% Cl: 18.07, 23.20) (HR=0.62 [95% Cl: 0.50, 0.77]). These data were initially reported at the 57th American Society of Hematology Annual Meeting in December 2015.
The most common adverse reactions (all grades) in ERd and Rd (>10%), respectively, were diarrhea (59.2%, 49.3%), pyrexia (43.0%, 27.7%), fatigue (40.0%, 34.7%), cough (33.2%, 20.3%), nasopharyngitis (29.5%, 27.7%), upper respiratory tract infection (25.2%, 22.7%), lymphopenia (17.6%, 13.6%), headache (17.2%, 9.6%), pneumonia (15.6%, 12.9%) and herpes zoster (10.0%, 5.7%).

"Today's decision of the European Commission is excellent news for relapsed and refractory multiple myeloma patients," said Sarper Diler, President of Myeloma Patients Europe. "Multiple myeloma has had a difficult-to-treat history, and at Myeloma Patients Europe, we are committed to ensuring these patients living in any European country are able to access new, innovative medicines, like Empliciti."

"Empliciti represents an important new treatment option for patients with multiple myeloma and healthcare providers who are treating this cancer in Europe," said Michael Severino, M.D., executive vice president of research and development and chief scientific officer, AbbVie. "AbbVie is proud to be part of the team that developed Empliciti and pleased to be partnering with Bristol-Myers Squibb to bring this new therapy to previously treated multiple myeloma patients."

**About ELOQUENT-2**

ELOQUENT-2 (CA204-004) is a Phase 3, open-label, randomized study evaluating Empliciti in combination with Rd versus Rd alone in patients with relapsed or refractory multiple myeloma. The trial randomized 646 patients who had received one to three prior therapies. Patients were randomized 1:1 to receive either Empliciti 10 mg/kg in combination with Rd or Rd alone in 4-week cycles until disease progression or unacceptable toxicity. Baseline patient demographics and disease characteristics were well balanced between treatment arms and included a meaningful portion of patients who were ≥ 65 years old, had high-risk cytogenetics and/or were refractory to the most recent line of therapy. The minimum follow-up for all study subjects was 24 months. The co-primary endpoints were PFS, as assessed by hazard ratio, and ORR, as determined by a blinded Independent Review Committee using the European Group for Blood and Marrow Transplantation response criteria.

"As multiple myeloma is largely incurable and is often characterized by a cycle of remission and relapse, there is a critical need for new therapies for patients that work in unique and innovative ways," said Antonio Palumbo, M.D., study investigator and chief of the Myeloma Unit, Department of Oncology, University of Torino in Torino, Italy. "In clinical trials, Empliciti in combination with lenalidomide and dexamethasone delivered a significant benefit in progression-free survival compared to lenalidomide and dexamethasone alone, which could make a meaningful difference in the lives of patients struggling with this serious disease."

Discontinuation rates due to adverse reactions were similar across the Erd and Rd arms (8.7%, 12.9%). The most frequent serious adverse reactions (Grade 3-4) in Erd and Rd were lymphopenia (12.7%, 7.4%), pneumonia (10.5%, 8.1%), fatigue (6.4%, 6.2%), diarrhea (3.7%, 3.1%) and deep vein thrombosis (3.5%, 1.7%). The most common adverse reactions in Erd and Rd (>20%), respectively, were diarrhea (59.2%, 49.3%), pyrexia (43.0%, 27.7%), fatigue (40.0%, 34.7%), cough (33.2%, 20.3%), nasopharyngitis (29.5%, 27.7%) and upper respiratory tract infection (25.2%, 22.7%).

Infusion reactions occurred in 10% of patients treated with ERd; these adverse reactions were Grade 3 or lower (Grade 3, 25.2%, Grade 4, 0%). In the trial, 1% of patients discontinued due to infusion reactions, and 5% of patients required interruption of the administration of Empliciti for a median of 25 minutes.

**About Multiple Myeloma**

Multiple myeloma is a hematologic, or blood, cancer that develops in the bone marrow. It occurs when a plasma cell, a type of cell in the soft center of bone marrow, becomes cancerous and multiplies uncontrollably. Common symptoms of multiple myeloma include bone pain, fatigue, kidney impairment and infections.

Despite advances in multiple myeloma treatment over the last decade, less than half of patients survive for five or more years after diagnosis. Patients often experience a cycle of remission and relapse, and once a patient first relapses, their prognosis worsens with progressively faster relapses through each subsequent line of therapy. It is estimated that annually, more than 114,200 new cases of multiple myeloma are diagnosed, and more than 80,000 people die from the disease globally.

**Bristol-Myers Squibb & Immuno-Oncology: Advancing Oncology Research**

At Bristol-Myers Squibb, we have a vision for the future of cancer care that is focused on Immuno-Oncology, now considered a major treatment modality alongside surgery, radiation and chemotherapy for certain types of cancer.

We have a comprehensive clinical portfolio of investigational and approved Immuno-Oncology agents, many of which were discovered and developed by our scientists. We pioneered the research leading to the first regulatory approval for the combination of two Immuno-Oncology agents and continue to study the role of combinations in cancer.

Our collaboration with academia, as well as small and large biotech companies, is responsible for researching the potential Immuno-Oncology and non-Immuno-Oncology combinations, with the goal of providing new treatment options in clinical practice.

At Bristol-Myers Squibb, we are committed to changing survival expectations in hard-to-treat cancers and the way patients live with cancer.

**About Empliciti**

Empliciti is an immunostimulatory antibody that specifically targets Signaling Lymphocyte Activation Molecule Family member 7 (SLAMF7), a cell-surface glycoprotein. SLAMF7 is expressed on myeloma cells independent of cytogenetic abnormalities. SLAMF7 also is expressed on Natural Killer cells, plasma cells and at lower levels on specific immune cell subsets of differentiated cells within the hematopoietic lineage.

Empliciti has a dual mechanism of action. It directly activates the immune system through Natural Killer cells via the SLAMF7 pathway. Empliciti also targets SLAMF7 on myeloma cells, tagging these malignant cells for destruction by the immune system.
**EMPLICITI** (elotuzumab) is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior therapies.

**U.S. INDICATION**

**EMPLICITI™** (elotuzumab) is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior therapies.

**U.S. IMPORTANT SAFETY INFORMATION**

**Infusion Reactions**
- EMPLICITI can cause infusion reactions. Common symptoms include fever, chills, and hypertension. Bradycardia and hypotension also developed during infusions. In the trial, 5% of patients required interruption of the administration of EMPLICITI for a median of 25 minutes due to infusion reactions, and 1% of patients discontinued due to infusion reactions. Of the patients who experienced an infusion reaction, 70% (23/33) had them during the first dose. If a Grade 2 or higher infusion reaction occurs, interrupt the EMPLICITI infusion and institute appropriate medical and supportive measures. If the infusion reaction recurs, stop the EMPLICITI infusion and do not restart it on that day. Severe infusion reactions may require permanent discontinuation of EMPLICITI therapy and emergency treatment.
- Premedicate with dexamethasone, H1 Blocker, H2 Blocker, and acetaminophen prior to infusing with EMPLICITI.

**Infections**
- In a clinical trial of patients with multiple myeloma (N=635), infections were reported in 81.4% of patients in the EMPLICITI with lenalidomide/dexamethasone arm (ERd) and 74.4% in the lenalidomide/dexamethasone arm (Rd). Grade 3-4 infections were 28% (ERd) and 24.3% (Rd). Opportunistic infections were reported in 22% (ERd) and 12.9% (Rd). Fungal infections were 9.7% (ERd) and 5.4% (Rd). Herpes zoster was 13.5% (ERd) and 6.9% (Rd). Discontinuations due to infections were 3.5% (ERd) and 4.1% (Rd). Fatal infections were 2.5% (ERd) and 2.2% (Rd). Monitor patients for development of infections and treat promptly.

**Second Primary Malignancies**
- In a clinical trial of patients with multiple myeloma (N=635), invasive second primary malignancies (SPM) were 9.1% (ERd) and 5.7% (Rd). The rate of hematologic malignancies were the same between ERd and Rd treatment arms (1.6%). Solid tumors were reported in 3.5% (ERd) and 2.2% (Rd). Skin cancer was reported in 4.4% (ERd) and 2.8% (Rd). Monitor patients for the development of SPMs.

**Hepatotoxicity**
- Elevations in liver enzymes (AST/ALT greater than 3 times the upper limit, total bilirubin greater than 2 times the upper limit, and alkaline phosphatase less than 2 times the upper limit) consistent with hepatotoxicity were 2.5% (ERd) and 0.6% (Rd). Two patients experiencing hepatotoxicity discontinued treatment; however, 6 out of 8 patients had resolution and continued treatment. Monitor liver enzymes periodically. Stop EMPLICITI upon Grade 3 or higher elevation of liver enzymes. After return to baseline values, continuation of treatment may be considered.

**Interference with Determination of Complete Response**
- EMPLICITI is a humanized IgG kappa monoclonal antibody that can be detected on both the serum protein electrophoresis and immunofixation assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and possibly relapse from complete response in patients with IgG kappa myeloma protein.

**Pregnancy/Females and Males of Reproductive Potential**
- There are no studies with EMPLICITI with pregnant women to inform any drug associated risks.
- There is a risk of fetal harm, including severe life-threatening human birth defects associated with lenalidomide and it is contraindicated for use in pregnancy. Refer to the lenalidomide full prescribing information for requirements regarding contraception and the prohibitions against blood and/or sperm donation due to presence and transmission in blood and/or semen and for additional information.

**Adverse Reactions**
- Infusion reactions were reported in approximately 10% of patients treated with EMPLICITI with lenalidomide and dexamethasone. All reports of infusion reaction were Grade 3 or lower. Grade 3 infusion reactions occurred in 1% of patients.
- Serious adverse reactions were 65.4% (ERd) and 56.5% (Rd). The most frequent serious adverse reactions in the ERd arm compared to the Rd arm were: pneumonia (15.4%, 11%), pyrexia (6.9%, 4.7%), respiratory tract infection (3.1%, 1.3%), anemia (2.8%, 1.9%), pulmonary embolism (3.1%, 2.5%), and acute renal failure (2.5%, 1.9%).
- The most common adverse reactions in ERd and Rd, respectively (>20%) were fatigue (61.6%, 51.7%), diarrhea (46.9%, 36.0%), pyrexia (37.4%, 24.6%), constipation (35.5%, 27.1%), cough (34.3%, 18.9%), peripheral neuropathy (26.7%, 20.8%), nasopharyngitis (24.5%, 19.2%), upper respiratory tract infection (22.6%, 17.4%), decreased appetite (20.8%, 12.6%), and pneumonia (20.1%, 14.2%).

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Please see the full Prescribing Information for Empliciti.

About Bristol-Myers Squibb

Bristol-Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. For more information about Bristol-Myers Squibb, visit us at BMS.com or follow us on LinkedIn, Twitter, YouTube and Facebook.

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, Follow @abbvie on Twitter or view careers on our Facebook or LinkedIn page.

Bristol-Myers Squibb Forward-Looking Statement

This press release contains “forward-looking statements” as that term is defined in the Private Securities Litigation Reform Act of 1995 regarding the research, development and commercialization of pharmaceutical products. Such forward-looking statements are based on current expectations and involve inherent risks and uncertainties, including factors that could delay, divert or change any of them, and could cause actual outcomes and results to differ materially from current expectations. No forward-looking statement can be guaranteed. Forward-looking statements in this press release should be evaluated together with the many uncertainties that affect Bristol-Myers Squibb’s business, particularly those identified in the cautionary factors discussion in Bristol-Myers Squibb’s Annual Report on Form 10-K for the year ended December 31, 2015 in our Quarterly Reports on Form 10-Q and our Current Reports on Form 8-K. Bristol-Myers Squibb undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.

AbbVie 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.

Endnotes

Empliciti is a trademark of Bristol-Myers Squibb Company.

Revlimid is a registered trademark of Celgene Corporation. All other trademarks are property of their respective owners.

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