Bristol-Myers Squibb Receives Positive Decision from National Institute of Health and Clinical Excellence (NICE) for YERVOY® (ipilimumab)

The Associated Press

PRINCETON, N.J.--(BUSINESS WIRE)--Nov 1, 2012--Bristol-Myers Squibb Company (NYSE: BMY) is pleased to announce that today the National Institute of Health and Clinical Excellence (NICE) has decided to recommend YERVOY ® (ipilimumab), which is approved in the European Union for the treatment of previously-treated metastatic (advanced) melanoma, within the Final Appraisal Determination (FAD). This important decision will enable eligible patients in England and Wales to routinely access treatment with YERVOY through the National Health Services (NHS).

“Today’s decision is very welcome news and marks a major milestone in the treatment of advanced melanoma,” said Dr. Paul Lorigan, Senior Lecturer in Medical Oncology, the Christie NHS Foundation Trust. “Ipilimumab’s potential to provide a long-term survival benefit in some patients makes it an important treatment option and represents a genuine step change in the management of this disease.” Metastatic melanoma is the deadliest form of skin cancer with an average life expectancy of just six to nine months and a one-year mortality rate of 75%. YERVOY is the only approved treatment for metastatic melanoma to deliver a durable long-term survival benefit at two years for 24 percent of patients. In the pivotal study, which included more than 4.5 years of follow up, median overall survival was 10 months (95% CI: 8.0-13.8) for YERVOY and 6 months (95% CI: 5.5-8.7) for the gp100 control arm. Five-year follow up results from three Phase 2 exploratory studies were recently presented during the European Society of Medical Oncology congress (September 12 – October 2), adding to the growing body of long-term survival data for YERVOY in metastatic melanoma.

Overall, the types of adverse events (AEs) attributed to YERVOY are generally mechanism (immune)- based. YERVOY can result in severe and fatal immune-related adverse reactions due to T-cell activation and proliferation. Adverse events associated with YERVOY are managed with protocol-specific guidelines, including the administration of systemic corticosteroids, dose interruption/discontinuation and/or other immunosuppressants.

“Bristol-Myers Squibb is committed to leading advances in immuno-oncology, a field that is focused on harnessing the immune system to fight cancer and one that is increasingly recognized as a fourth pillar of the cancer-treatment platform,” said Beatrice Cazala, executive vice president, commercial operations, Bristol-Myers Squibb. “YERVOY, the first-approved compound from our immuno-oncology pipeline, exemplifies how this type of medical innovation can address a significant unmet clinical need. We are pleased that our close collaboration with NICE on this appraisal over the past year has resulted in an outcome that is in the best interest of

patients. Today's decision supports the UK government's statement that access to innovative medicines is a key driver for better patient outcomes." The NICE approval follows the provision of access to treatment with YERVOY for previously-treated advanced melanoma patients in an increasing number of European countries, including Spain, Germany, Austria, Switzerland, Denmark, Luxembourg, Belgium, Finland, Netherlands, Ireland and Sweden. Bristol-Myers Squibb is working closely with other European authorities to secure further access to YERVOY to address the unmet need.

Immuno-Oncology at Bristol-Myers Squibb Historically, common approaches to cancer treatment have included surgery, radiation and chemotherapy or systemic therapy. However, recent advances in the development of immunotherapies have provided further scientific evidence that these novel agents play a role in mediating cancer regression. This, coupled with the increasing use of immunotherapies, has resulted in the recognition of immunotherapy as a fourth pillar of the cancer-treatment platform.

Immuno-oncology, which focuses on the scientific potential of harnessing the unique properties of the immune system to fight cancer, is a prioritized area of research and development at Bristol-Myers Squibb. The Company is committed to leading advances in this important field of research and is exploring a variety of innovative compounds and immunotherapeutic approaches to help address significant unmet medical needs in a broad range of cancers. More information can be found at www.BMSImmunoOncology.com.

About YERVOY In March 2011, the FDA approved YERVOY 3 mg/kg monotherapy for patients with unresectable or metastatic melanoma. It received regulatory approval in the European Union in July 2011 for previously-treated metastatic (advanced) melanoma, making it the first medicine to be licensed in the UK for the treatment of this disease since dacarbazine in 1970. YERVOY is now approved in 41 countries worldwide.

In October, YERVOY received the prestigious Prix Galien USA 2012 Award for Best Biotechnology Product. The Prix Galien Awards were created to honor medical research and pharmacology for outstanding efforts to improve the human condition through approval of innovative treatments and medicines.

YERVOY, which is a recombinant, human monoclonal antibody, is the first-approved cancer immunotherapy that blocks the cytotoxic T- lymphocyte antigen-4 (CTLA-4). CTLA-4 is a negative regulator of T-cell activation. Ipilimumab binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation. The mechanism of action of ipilimumab's effect in patients with melanoma is indirect, possibly through T-cell mediated anti-tumor immune responses.

U.S. Indication and Important Safety Information WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS YERVOY can result in severe and fatal immune-mediated adverse reactions due to T-cell activation and proliferation. These immune-mediated reactions may involve any organ system; however, the most common

severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy. The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of YERVOY. Assess patients for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy and evaluate clinical chemistries including liver function tests (LFTs) and thyroid function tests at baseline and before each dose. Permanently discontinue YERVOY for any of the following: Persistent moderate adverse reactions or inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day Failure to complete full treatment course within 16 weeks from administration of first dose Severe or life-threatening adverse reactions, including any of the following Colitis with abdominal pain, fever, ileus, or peritoneal signs; increase in stool frequency (≥7 over baseline), stool incontinence, need for intravenous hydration for >24 hours, gastrointestinal hemorrhage, and gastrointestinal perforationAST or ALT >5 × the upper limit of normal (ULN) or total bilirubin >3 × the ULNStevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full-thickness dermal ulceration or necrotic, bullous, or hemorrhagic manifestationsSevere motor or sensory neuropathy, Guillain-Barré syndrome, or myasthenia gravisSevere immune-mediated reactions involving any organ systemImmune-mediated ocular disease which is unresponsive to topical immunosuppressive therapy Immune-mediated Enterocolitis: In the pivotal Phase 3 study in YERVOY-treated patients, severe, life-threatening or fatal (diarrhea of ≥7 stools above baseline, fever, ileus, peritoneal signs; Grade 3-5) immune-mediated enterocolitis occurred in 34 (7%) and moderate (diarrhea with up to 6 stools above baseline, abdominal pain, mucus or blood in stool; Grade 2) enterocolitis occurred in 28 (5%) patients Across all YERVOY-treated patients (n=511), 5 (1%) developed intestinal perforation, 4 (0.8%) died as a result of complications, and 26 (5%) were hospitalized for severe enterocolitis Infliximab was administered to 5 of 62 (8%) patients with moderate, severe, or life-threatening immune-mediated enterocolitis following inadequate response to corticosteroids Monitor patients for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, mucus or blood in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic patients, rule out infectious etiologies and consider endoscopic evaluation for persistent or severe symptoms Permanently discontinue YERVOY in patients with severe enterocolitis and initiate systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent). Upon improvement to ≤Grade 1, initiate corticosteroid taper and continue over at least 1 month. In clinical trials, rapid corticosteroid tapering resulted in recurrence or worsening symptoms of enterocolitis in some patients Withhold YERVOY for moderate enterocolitis; administer anti-diarrheal treatment and, if persistent for >1 week, initiate systemic corticosteroids (0.5 mg/kg/day prednisone or equivalent) Immune-mediated Hepatitis: In the pivotal Phase 3 study in YERVOY-treated patients, severe, life-threatening, or fatal hepatotoxicity (AST or ALT elevations >5x the ULN or total bilirubin elevations >3x the ULN; Grade 3–5) occurred in 8 (2%) patients , with fatal hepatic failure in 0.2% and hospitalization in 0.4% 13 (2.5%) additional YERVOY-treated patients experienced moderate hepatotoxicity manifested by LFT abnormalities (AST or ALT elevations >2.5x but ≤5x the ULN or total bilirubin elevation >1.5x but ≤3x the ULN; Grade 2) Monitor LFTs (hepatic transaminase and bilirubin levels) and assess patients for signs and symptoms of hepatotoxicity

before each dose of YERVOY. In patients with hepatotoxicity, rule out infectious or malignant causes and increase frequency of LFT monitoring until resolution Permanently discontinue YERVOY in patients with Grade 3-5 hepatotoxicity and administer systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent). When LFTs show sustained improvement or return to baseline, initiate corticosteroid tapering and continue over 1 month. Across the clinical development program for YERVOY, mycophenolate treatment has been administered in patients with persistent severe hepatitis despite high-dose corticosteroids Withhold YERVOY in patients with Grade 2 hepatotoxicity Immune-mediated Dermatitis: In the pivotal Phase 3 study in YERVOY-treated patients, severe, life-threatening or fatal immune-mediated dermatitis (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations; Grade 3–5) occurred in 13 (2.5%) patients 1 (0.2%) patient died as a result of toxic epidermal necrolysis1 additional patient required hospitalization for severe dermatitis There were 63 (12%) YERVOY-treated patients with moderate (Grade 2) dermatitis Monitor patients for signs and symptoms of dermatitis such as rash and pruritus. Unless an alternate etiology has been identified, signs or symptoms of dermatitis should be considered immune-mediated Permanently discontinue YERVOY in patients with severe, life-threatening, or fatal immune-mediated dermatitis (Grade 3-5). Administer systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent). When dermatitis is controlled, corticosteroid tapering should occur over a period of at least 1 month. Withhold YERVOY in patients with moderate to severe signs and symptoms Treat mild to moderate dermatitis (e.g., localized rash and pruritus) symptomatically. Administer topical or systemic corticosteroids if there is no improvement within 1 week Immune-mediated Neuropathies: In the pivotal Phase 3 study in YERVOY-treated patients, 1 case of fatal Guillain-Barré syndrome and 1 case of severe (Grade 3) peripheral motor neuropathy were reported Across the clinical development program of YERVOY, myasthenia gravis and additional cases of Guillain-Barré syndrome have been reported Monitor for symptoms of motor or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or paresthesia. Permanently discontinue YERVOY in patients with severe neuropathy (interfering with daily activities) such as Guillain-Barré–like syndromes Institute medical intervention as appropriate for management of severe neuropathy. Consider initiation of systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent) for severe neuropathies. Withhold YERVOY in patients with moderate neuropathy (not interfering with daily activities) Immune-mediated Endocrinopathies: In the pivotal Phase 3 study in YERVOY- treated patients, severe to life-threatening immune-mediated endocrinopathies (requiring hospitalization, urgent medical intervention, or interfering with activities of daily living; Grade 3-4) occurred in 9 (1.8%) patients All 9 patients had hypopituitarism, and some had additional concomitant endocrinopathies such as adrenal insufficiency, hypogonadism, and hypothyroidism.6 of the 9 patients were hospitalized for severe endocrinopathies Moderate endocrinopathy (requiring hormone replacement or medical intervention; Grade 2) occurred in 12 (2.3%) YERVOY-treated patients and consisted of hypothyroidism, adrenal insufficiency, hypopituitarism, and 1 case each of hyperthyroidism and Cushing’s syndrome Median time to onset of moderate to severe immune-mediated endocrinopathy was 11 weeks and ranged up to 19.3 weeks after the initiation of YERVOY Monitor patients for clinical signs and

symptoms of hypophysitis, adrenal insufficiency (including adrenal crisis), and hyper- or hypothyroidism Patients may present with fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may resemble other causes such as brain metastasis or underlying disease. Unless an alternate etiology has been identified, signs or symptoms should be considered immune-mediatedMonitor thyroid function tests and clinical chemistries at the start of treatment, before each dose, and as clinically indicated based on symptoms. In a limited number of patients, hypophysitis was diagnosed by imaging studies through enlargement of the pituitary gland Withhold YERVOY in symptomatic patients. Initiate systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent) and initiate appropriate hormone replacement therapy. Long-term hormone replacement therapy may be necessary Other Immune-mediated Adverse Reactions, Including Ocular Manifestations: In the pivotal Phase 3 study in YERVOY-treated patients, clinically significant immune-mediated adverse reactions seen in <1% were: nephritis, pneumonitis, meningitis, pericarditis, uveitis, iritis, and hemolytic anemia Across the clinical development program for YERVOY, immune-mediated adverse reactions also reported with <1% incidence were: myocarditis, angiopathy, temporal arteritis, vasculitis, polymyalgia rheumatica, conjunctivitis, blepharitis, episcleritis, scleritis, leukocytoclastic vasculitis, erythema multiforme, psoriasis, pancreatitis, arthritis, and autoimmune thyroiditis Permanently discontinue YERVOY for clinically significant or severe immune-mediated adverse reactions. Initiate systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent) for severe immune-mediated adverse reactions Administer corticosteroid eye drops for uveitis, iritis, or episcleritis. Permanently discontinue YERVOY for immune-mediated ocular disease unresponsive to local immunosuppressive therapy Pregnancy & Nursing: YERVOY is classified as pregnancy category C. There are no adequate and well-controlled studies of YERVOY in pregnant women. Use YERVOY during pregnancy only if the potential benefit justifies the potential risk to the fetus Human IgG1 is known to cross the placental barrier and YERVOY is an IgG1; therefore, YERVOY has the potential to be transmitted from the mother to the developing fetus It is not known whether YERVOY is secreted in human milk. Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from YERVOY, a decision should be made whether to discontinue nursing or to discontinue YERVOY Common Adverse Reactions: The most common adverse reactions (≥5%) in patients who received YERVOY at 3 mg/kg were fatigue (41%), diarrhea (32%), pruritus (31%), rash (29%), and colitis (8%) Please see full Prescribing Information, including Boxed WARNING regarding immune-mediated adverse reactions available at.

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 www.bms.com, or follow us on Twitter at http://twitter.com/bmsnews.

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