



FDA Approves IXEMPRA™ (Ixabepilone), a Semi-Synthetic Analog of Epothilone B, for the Treatment of Advanced Breast Cancer

Tuesday, October 16, 2007 8:00 am EDT

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE: BMY) announced today that the U.S. Food and Drug Administration (FDA) has granted approval of IXEMPRA™ (ixabepilone) as monotherapy for the treatment of patients with metastatic or locally advanced breast cancer in patients whose tumors are resistant or refractory to anthracyclines, taxanes, and capecitabine. The FDA has also granted approval of IXEMPRA in combination with capecitabine for the treatment of patients with metastatic or locally advanced breast cancer resistant to treatment with an anthracycline, and a taxane, or whose cancer is taxane resistant and for whom further anthracycline therapy is contraindicated. IXEMPRA is a microtubule inhibitor belonging to a class of antineoplastic agents, the epothilones. Bristol-Myers Squibb anticipates that IXEMPRA will be available within days.

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"Previously, patients with aggressive metastatic or locally advanced breast cancer no longer responding to currently available chemotherapies had limited treatment options," said Linda Vahdat, M.D., Associate Professor of Clinical Medicine and Associate Attending Physician, New York-Presbyterian Hospital/Weill Cornell Medical Center. "The approval of IXEMPRA means that we now have an important new option for patients with metastatic breast cancer who have rapidly progressed through currently approved chemotherapies."

"Bristol-Myers Squibb has a rich history in oncology spanning more than 40 years, and we are extremely proud that IXEMPRA has been approved as it is a significant addition to the Bristol-Myers Squibb oncology portfolio and addresses a serious unmet medical need in the treatment of patients with metastatic or locally advanced breast cancer," said Elliott Sigal, M.D., Ph.D., Executive Vice President, Chief Scientific Officer and President, Research and Development, Bristol-Myers Squibb.

Registrational Trials

The FDA reviewed the efficacy and safety of IXEMPRA based on the analysis of two multi-center, multinational trials that included 878 patients and evaluated IXEMPRA either as a monotherapy or in combination with capecitabine in patients with metastatic or locally advanced breast cancer.

(Phase II, Monotherapy Trial: -081) The single-arm Phase II trial evaluated the efficacy and safety of IXEMPRA as a monotherapy. This study enrolled 126 patients with metastatic or locally advanced breast cancer resistant to three prior therapies (an anthracycline, a taxane and capecitabine). Resistance was defined as disease progression while on therapy in the metastatic setting (defined as progression while on treatment or within eight weeks of last dose) or recurrence within six months of the last dose in the adjuvant or neoadjuvant setting (only for

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anthracycline and taxane). HER2 positive patients must also have progressed during or after discontinuation of trastuzumab. The primary endpoint was objective response rate, which is an assessment of tumor shrinkage in response to treatment. Results determined by an independent radiology review (IRR) showed an objective partial response of 12.4% (95% CI, 6.9-19.9) in 113 response-evaluable patients.

Treatment-related non-hematological adverse events (greater than or equal to 20%) included: peripheral sensory neuropathy 62% (Grade 3/4: 14%), fatigue/asthenia 56% (Grade 3/4: 13%), myalgia/arthralgia 49% (Grade 3/4: 8%), alopecia 48% (Grade 3/4: 0%), nausea 42% (Grade 3/4: 2%), stomatitis/mucositis 29% (Grade 3/4: 6%), vomiting 29% (Grade 3/4: 1%), diarrhea 22% (Grade 3/4: 1%), and musculoskeletal pain 20% (Grade 3/4: 3%). Treatment-related hematological adverse events (greater than or equal to 20%) included: neutropenia (Grade 3/4: 54%) and leukopenia (Grade 3/4: 49%).

(Phase III, Combination Trial: -046) The randomized Phase III trial evaluated the efficacy and safety of IXEMPRA in combination with capecitabine in comparison with capecitabine as monotherapy. This trial included 752 patients who were previously treated with anthracyclines and taxanes, and whose tumors had demonstrated prior resistance to these therapies. Anthracycline resistance is defined as progression while on therapy or within six months in the adjuvant setting, or three months in the metastatic setting. Taxane resistance is defined as progression while on therapy or within 12 months in the adjuvant setting or four months in the metastatic setting. Evaluation of the primary endpoint demonstrated that IXEMPRA in combination with capecitabine resulted in a statistically significant improvement in progression-free survival compared to capecitabine monotherapy - median 5.7 (95% CI, 4.8-6.7) vs. 4.1 months (95% CI, 3.1-4.3); $P < 0.0001$, Hazard ratio=0.69 (95% CI, 0.58-0.83).

Treatment-related non-hematological adverse events (greater than or equal to 20%) reported in patients treated with IXEMPRA in combination with capecitabine included: peripheral sensory neuropathy 65% (Grade 3/4: 21%), palmar-plantar erythrodysesthesia (hand-foot) syndrome 64% (Grade 3/4: 18%), fatigue/asthenia 60% (Grade 3/4: 16%), nausea 53% (Grade 3/4: 3%), diarrhea 44% (Grade 3/4: 6%), vomiting 39% (Grade 3/4: 4%), myalgia/arthralgia 39% (Grade 3/4: 8%), anorexia 34% (Grade 3/4: 3%), stomatitis/mucositis 31% (Grade 3/4: 4%), alopecia 31% (Grade 3/4: 0%), abdominal pain 24% (Grade 3/4: 2%), nail disorder 24% (Grade 3/4: 2%), musculoskeletal pain 23% (Grade 3/4: 2%), and constipation 22% (Grade 3/4: 0%). Treatment-related hematological adverse events (greater than or equal to 20%) reported in patients treated with IXEMPRA in combination with capecitabine included: neutropenia (Grade 3/4: 68%) and leukopenia (Grade 3/4: 57%).

Comparative treatment-related non-hematological adverse events reported in patients treated with capecitabine alone included: peripheral sensory neuropathy 16% (Grade 3/4: 0%), palmar-plantar erythrodysesthesia (hand-foot syndrome) 63% (Grade 3/4: 17%), fatigue/asthenia 29% (Grade 3/4: 4%), nausea 40% (Grade 3/4: 2%), diarrhea 39% (Grade 3/4: 9%), vomiting 24% (Grade 3/4: 2%), myalgia/arthralgia 5% (Grade 3/4: <1%), anorexia 15% (Grade 3/4: 1%), stomatitis/mucositis 20% (Grade 3/4: 3%), alopecia 3% (Grade 3/4: 0%), abdominal pain 14% (Grade 3/4: 1%), nail disorder 10% (Grade 3/4: <1%), musculoskeletal pain 5% (Grade 3/4: 0%), and constipation 6% (Grade 3/4: <1%). Treatment-related hematological adverse events of Grade 3/4 severity reported in patients treated with capecitabine alone included: neutropenia 11% and leukopenia 6%.

TOXICITY IN HEPATIC IMPAIRMENT

IXEMPRA (ixabepilone) in combination with capecitabine is contraindicated in patients with AST or ALT >2.5 x ULN or bilirubin >1 x ULN due to increased risk of toxicity and neutropenia-related death.

In combination with capecitabine, the overall frequency of Grade 3/4 adverse reactions, febrile neutropenia, serious adverse reactions, and toxicity related deaths was greater in patients with hepatic impairment.

Caution should be used when using IXEMPRA as monotherapy in patients with AST or ALT > 5 x ULN. Use of IXEMPRA in patients with AST or ALT > 10 x ULN or bilirubin >3 x ULN is not recommended.

With monotherapy, Grade 4 neutropenia, febrile neutropenia, and serious adverse reactions were more frequent in patients with hepatic impairment.

CONTRAINDICATIONS

IXEMPRA is contraindicated in patients:

-- with a known history of a severe (CTC Grade 3/4) hypersensitivity reaction to agents containing Cremophor® EL or its derivatives such as polyoxyethylated castor oil.

-- who have a baseline neutrophil count <1500 cells/mm³ or a platelet count <100,000 cells/mm³.

PERIPHERAL NEUROPATHY

Patients treated with IXEMPRA should be monitored for symptoms of neuropathy, such as burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, or neuropathic pain. Patients experiencing new or worsening peripheral neuropathy may require changes in the dose or discontinuation of IXEMPRA. Neuropathy was the most frequent cause of treatment discontinuation due to drug toxicity. Caution should be used when treating patients with diabetes mellitus or existing moderate to severe neuropathy.

MYELOSUPPRESSION

Patients should be monitored for myelosuppression; frequent peripheral blood cell counts are recommended for all patients receiving IXEMPRA.

Patients who experience severe neutropenia or thrombocytopenia should have their dose reduced. Neutropenia related deaths occurred in patients administered IXEMPRA and capecitabine (1.9% of 414 patients) and IXEMPRA alone (0.4% in 240 patients).

HYPERSENSITIVITY REACTION

Premedicate with an H1 and an H2 antagonist approximately 1 hour before IXEMPRA infusion and observe for hypersensitivity reactions (e.g., flushing, rash, dyspnea, and bronchospasm).

In case of severe hypersensitivity reactions, infusion of IXEMPRA should be stopped and aggressive supportive treatment (e.g., epinephrine, corticosteroids) started.

Patients who experience a hypersensitivity reaction in one cycle of IXEMPRA must be premedicated in subsequent cycles with a corticosteroid in addition to the H1

PREGNANCY

Women should be advised not to become pregnant when taking IXEMPRA. If this drug is used during pregnancy or the patient becomes pregnant, the patient should be apprised of the potential hazard to the fetus.

CARDIAC ADVERSE REACTIONS

Caution should be exercised in patients with a history of cardiac disease. Discontinuation of IXEMPRA should be considered in patients who develop cardiac ischemia or impaired cardiac function due to reports of cardiovascular adverse reactions (e.g., myocardial ischemia, supraventricular arrhythmia, and ventricular dysfunction). The frequency of cardiac adverse reactions (myocardial ischemia and ventricular dysfunction) was higher in the IXEMPRA in combination with capecitabine (1.9%) than in the capecitabine alone (0.3%) treatment group.

POTENTIAL FOR COGNITIVE IMPAIRMENT FROM EXCIPIENTS

IXEMPRA contains dehydrated alcohol USP. Consideration should be given to the possibility of central nervous system and other effects of alcohol.

ADVERSE REACTIONS

The most common adverse reactions (greater than or equal to 20%) reported by patients receiving IXEMPRA were peripheral sensory neuropathy, fatigue/asthenia, myalgia/arthralgia, alopecia, nausea, vomiting, stomatitis/mucositis, diarrhea, and musculoskeletal pain. The following additional events occurred in greater than or equal to 20% in combination treatment: palmar-plantar erythrodysesthesia (hand-foot) syndrome, anorexia, abdominal pain, nail disorder, and constipation. Drug-associated hematologic abnormalities (>40%) include neutropenia, leukopenia, anemia, and thrombocytopenia.

[Please see accompanying full Prescribing Information](#) including **boxed WARNING** regarding hepatic impairment.

About Bristol-Myers Squibb

For more than 40 years, Bristol-Myers Squibb has been committed to building a unified vision for the future of cancer treatment. With expertise, dedication and resolve, that vision led to the development of a diverse global portfolio of anti-cancer therapies that are an important cornerstone of care today. Hundreds of scientists in Bristol-Myers Squibb's Research & Development organization are studying ways to improve current cancer treatments and identify better, more effective medicines for the future. Bristol-Myers Squibb is a global pharmaceutical and related health care products company whose mission is to extend and enhance human life.

For more information regarding IXEMPRA, please call 1-888-IXEMPRA (1-888-493-6772) Monday through Friday 8:00 am-5:00 pm ET or visit <http://www.ixempira.com/>.

This press release contains "forward-looking statements" as that term is defined in the Private Securities Litigation Reform Act of 1995. 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. Among other risks, there can be no guarantee as to when IXEMPRA (ixabepilone) will be commercially available. Forward-looking statements in this press

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, 2006 and in our Quarterly Reports on Form 10-Q. Bristol-Myers Squibb undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.

SOURCE: Bristol-Myers Squibb Company

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