European Commission Approves Extended Indication For Amgen's Kyprolis® (Carfilzomib) For The Treatment Of Relapsed Multiple Myeloma Patients

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Head-to-Head Phase 3 Trial Demonstrated Superiority of Kyprolis and Dexamethasone Over Velcade® (Bortezomib) and Dexamethasone in Patients with Relapsed Multiple Myeloma

New Indication Allows Kyprolis to be Used in Combination with Dexamethasone Alone for Appropriate Patients

THOUSAND OAKS, Calif., July 3, 2016 /PRNewswire/ -- Amgen (NASDAQ:AMGN) today announced that the European Commission (EC) has approved a variation to the marketing authorization for Kyprolis® (carfilzomib) to include use in combination with dexamethasone alone for adult patients with multiple myeloma who have received at least one prior therapy. The extended indication marks the second approval for Kyprolis by the EC in less than a year.

"In the Phase 3 head-to-head trial, Kyprolis in combination with dexamethasone doubled the time patients lived without their cancer progressing, as well as the rates of complete response compared to bortezomib and dexamethasone," said Sean E. Harper, M.D., executive vice president of Research and Development at Amgen. "Kyprolis-based regimens have now shown superiority over two former standard-of-care treatment options for relapsed multiple myeloma patients, reinforcing Kyprolis' place as a foundational therapy in this patient population."

The EC approved the extended indication for Kyprolis based on data from the Phase 3 head-to-head ENDEAVOR trial in which patients with multiple myeloma treated with Kyprolis plus dexamethasone (Kd) achieved superior progression-free survival (PFS) of 18.7 months compared to 9.4 months in those receiving bortezomib plus dexamethasone (Vd) (HR=0.53; 95 percent CI: 0.44, 0.65; *p* <0.0001). Kd also demonstrated improvement over Vd for secondary endpoints, including rates of complete response or better, which were double in patients treated with Kd compared to those treated with Vd (12.5 percent vs. 6.2 percent, *p* <0.0001). The tolerability profile was similar in the two arms, however patients treated with Kd experienced a significantly lower rate of grade 2 or higher neuropathy events than those treated with Vd, a frequent dose-limiting toxicity in patients receiving bortezomib (6 percent [95 percent CI: 4, 8] vs. 32 percent [95 percent CI: 28, 36], respectively). The most common adverse reactions that occurred in greater than 20 percent of patients treated with Kyprolis were anemia, fatigue, diarrhea, thrombocytopenia, nausea, pyrexia, dyspnea, respiratory tract infection, cough and peripheral edema.

Kyprolis was first approved by the EC in November 2015 for use in combination with lenalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy based on results of the ASPIRE study. Today's approval by the EC follows the U.S. Food and Drug Administration's approval of a supplemental New Drug Application based on the ENDEAVOR results in January 2016.

Multiple myeloma is an incurable blood cancer, characterized by a recurring pattern of remission and relapse.[1] It is a rare and very aggressive disease that accounts for approximately one percent of all cancers worldwide.[2-4] In Europe, approximately 39,000 patients are diagnosed with multiple myeloma each year and 24,000 patient deaths are reported on an annual basis.[5]

About ENDEAVOR

The randomized ENDEAVOR (Randomiz**E**d, Ope**N** Label, Phase 3 Study of Carfilzomib Plus **DE**xameth**A**sone **V**s Bortezomib Plus Dexamethas**O**ne in Patients With **R**elapsed Multiple Myeloma) trial of 929 patients evaluated Kyprolis in combination with low-dose dexamethasone, vs. bortezomib with low-dose dexamethasone in patients whose multiple myeloma has relapsed after at least one, but not more than three prior therapeutic regimens. The primary endpoint of the trial was PFS, defined as the time from treatment initiation to disease progression or death. In a clinical trial, measuring the PFS is one way to demonstrate how well a treatment works.[6]

As stated above, Kyprolis with dexamethasone (Kd) was superior to bortezomib and dexamethasone (Vd) and demonstrated significantly longer PFS. Improvement in PFS in the Kd arm compared to the Vd arm was seen across key pre-specified subgroups, including bortezomib-naive patients, those with high- or standard-risk cytogenetics and with or without prior transplantation.

In terms of secondary endpoints, Kd achieved a higher overall response rate than Vd (76.9 percent vs. 62.6 percent; *p* <0.0001). In the Kyprolis and bortezomib groups, 54.3 percent and 28.6 percent of patients achieved a very good partial response or better (*p* <0.0001), respectively. Overall survival data are not yet mature and continue to be monitored.

Treatment discontinuation due to adverse events and on-study deaths were comparable between the two arms.[7] A number of known adverse drug reactions were reported at a higher rate in the Kyprolis group compared with the bortezomib group, including any-grade dyspnea, hypertension, pyrexia, and cough as were any-grade cardiac failure (grouped term; 8 percent vs. 3 percent) and acute renal failure (grouped term; 8 percent vs. 5 percent).[7]

Rates of grade 3 or higher adverse events were 73 percent in the Kyprolis group and 67 percent in the bortezomib group.[7] Grade 3 or higher adverse events of interest in the Kyprolis and bortezomib groups included hypertension (preferred term; 9 percent vs. 3 percent), dyspnea (preferred term; 5 percent vs. 2 percent), cardiac failure (grouped term; 5 percent vs. 2 percent), acute renal failure (grouped term; 4 percent vs. 3 percent), ischemic heart disease (grouped term; 2 percent vs. 2 percent) and pulmonary hypertension (grouped term; 0.6 percent vs. 0.2 percent).[7]

Patients received treatment until progression with Kyprolis as a 30-minute infusion on days 1, 2, 8, 9, 15 and 16 of a 28 day treatment cycle. Patients received low-dose dexamethasone (20 mg) orally or intravenously on days 1, 2, 8, 9, 15, 16, 22, and 23 of each treatment cycle. For Cycle 1 only, Kyprolis was administered at 20 mg/m^2 on days 1 and 2, and if tolerated followed by escalation to 56 mg/m^2 from day 8. Patients who tolerated 56 mg/m^2 in Cycle 1 were kept at this dose for subsequent cycles. Patients who received bortezomib (1.3 mg/m^2) with low-dose dexamethasone (20 mg) were administered bortezomib subcutaneously or intravenously at the discretion of the investigator and in accordance with regulatory approval of bortezomib. More than 75 percent of the patients in the control arm received bortezomib subcutaneously. This study was conducted at 235 sites

worldwide. For information about this trial, please visit www.clinicaltrials.gov under trial identification number NCT01568866.

About Kyprolis® (carfilzomib)

Proteasomes play an important role in cell function and growth by breaking down proteins that are damaged or no longer needed.[8] Kyprolis has been shown to block proteasomes, leading to an excessive build-up of proteins within cells.[8] In some cells, Kyprolis can cause cell death, especially in myeloma cells because they are more likely to contain a higher amount of abnormal proteins.[8,9]

Kyprolis is approved in the U.S. for the following:

- In combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy.
- As a single agent for the treatment of patients with relapsed or refractory multiple myeloma who have received one or more lines of therapy.

Kyprolis is also approved in Argentina, Israel, Kuwait, Mexico, Thailand, Colombia, Korea, Canada, Switzerland, Russia, Brazil and the European Union. Additional regulatory applications for Kyprolis are underway and have been submitted to health authorities worldwide.

For more U.S. information, please visit www.kyprolis.com.

Important EU Product Safety Information

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Kyprolis treatment should be supervised by a physician experienced in the use of anti-cancer therapy. The most serious side effects that may occur during Kyprolis treatment include: Cardiac toxicity, pulmonary toxicities, pulmonary hypertension, dyspnea, hypertension including hypertensive crises, acute renal failure, tumor lysis syndrome, infusion reactions, thrombocytopenia, hepatic toxicity, posterior reversible encephalopathy syndrome (PRES) and thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS). The most common side effects are anemia, fatigue, diarrhea, thrombocytopenia, nausea, pyrexia, dyspnea, respiratory tract infection, cough and peripheral edema.

Please refer to the Summary of Product Characteristics for full European prescribing information.

Important U.S. Product Safety Information

Cardiac Toxicities

- New onset or worsening of pre-existing cardiac failure (e.g., congestive heart failure, pulmonary edema, decreased ejection fraction), restrictive cardiomyopathy, myocardial ischemia, and myocardial infarction including fatalities have occurred following administration of KYPROLIS. Some events occurred in patients with normal baseline ventricular function. Death due to cardiac arrest has occurred within one day of KYPROLIS administration.
- Monitor patients for clinical signs or symptoms of cardiac failure or cardiac ischemia. Evaluate promptly if cardiac toxicity is suspected. Withhold KYPROLIS for Grade 3 or 4 cardiac adverse events until recovery, and consider whether to restart KYPROLIS at 1 dose level reduction based on a benefit/risk assessment.
- While adequate hydration is required prior to each dose in Cycle 1, monitor all patients for evidence of volume overload, especially patients at risk for cardiac failure. Adjust total fluid intake as clinically appropriate in patients with baseline cardiac failure or who are at risk for cardiac failure.
- Patients ≥ 75 years, the risk of cardiac failure is increased. Patients with New York Heart Association Class III and IV heart failure, recent myocardial infarction, conduction abnormalities, angina, or arrhythmias may be at greater risk for cardiac complications and should have a comprehensive medical assessment (including blood pressure and fluid management) prior to starting treatment with KYPROLIS and remain under close follow-up.

Acute Renal Failure

- Cases of acute renal failure and renal insufficiency adverse events (including renal failure) have occurred in patients receiving KYPROLIS. Acute renal failure was reported more frequently in patients with advanced relapsed and refractory multiple myeloma who received KYPROLIS monotherapy. Monitor renal function with regular measurement of the serum creatinine and/or estimated creatinine clearance. Reduce or withhold dose as appropriate.

Tumor Lysis Syndrome

- Cases of Tumor Lysis Syndrome (TLS), including fatal outcomes, have occurred in patients receiving KYPROLIS. Patients with multiple myeloma and a high tumor burden should be considered at greater risk for TLS. Adequate hydration is required prior to each dose in Cycle 1, and in subsequent cycles as needed. Consider uric acid lowering drugs in patients at risk for TLS. Monitor for evidence of TLS during treatment and manage promptly. Withhold KYPROLIS until TLS is resolved.

Pulmonary Toxicity

- Acute Respiratory Distress Syndrome (ARDS), acute respiratory failure, and acute diffuse infiltrative pulmonary disease such as pneumonitis and interstitial lung disease have occurred in patients receiving KYPROLIS. Some events have been fatal. In the event of drug-induced pulmonary toxicity, discontinue KYPROLIS.

Pulmonary Hypertension

- Pulmonary arterial hypertension (PAH) was reported in patients treated with KYPROLIS. Evaluate with cardiac imaging and/or other tests as indicated. Withhold KYPROLIS for PAH until resolved or returned to baseline and consider whether to restart KYPROLIS based on a benefit/risk assessment.

Dyspnea

- Dyspnea was reported in patients treated with KYPROLIS. Evaluate dyspnea to exclude cardiopulmonary conditions including cardiac failure and pulmonary syndromes. Stop KYPROLIS for Grade 3 or 4 dyspnea until resolved or returned to baseline. Consider whether to restart KYPROLIS based on a benefit/risk assessment.

Hypertension

- Hypertension, including hypertensive crisis and hypertensive emergency, has been observed with KYPROLIS. Some of these events have been fatal. Monitor blood pressure regularly in all patients. If hypertension cannot be adequately controlled, withhold KYPROLIS and evaluate. Consider whether to restart KYPROLIS based on a benefit/risk assessment.

Venous Thrombosis

- Venous thromboembolic events (including deep venous thrombosis and pulmonary embolism) have been observed with KYPROLIS. Thromboprophylaxis is recommended for patients being treated with the combination of KYPROLIS with dexamethasone or with lenalidomide plus dexamethasone. The thromboprophylaxis regimen should be based on an assessment of the patient's underlying risks.
- Patients using oral contraceptives or a hormonal method of contraception associated with a risk of thrombosis should consider an alternative method of effective contraception during treatment with KYPROLIS in combination with dexamethasone or lenalidomide plus dexamethasone.

Infusion Reactions

- Infusion reactions, including life-threatening reactions, have occurred in patients receiving KYPROLIS. Symptoms include fever, chills, arthralgia, myalgia, facial flushing, facial edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina. These reactions can occur immediately following or up to 24 hours after administration of KYPROLIS. Premedicate with dexamethasone to reduce the incidence and severity of infusion reactions. Inform patients of the risk and of symptoms of an infusion reaction and to contact a physician immediately if they occur.

Thrombocytopenia

- KYPROLIS causes thrombocytopenia with recovery to baseline platelet count usually by the start of the next cycle. Thrombocytopenia was reported in patients receiving KYPROLIS. Monitor platelet counts frequently during treatment with KYPROLIS. Reduce or withhold dose as appropriate.

Hepatic Toxicity and Hepatic Failure

- Cases of hepatic failure, including fatal cases, have been reported during treatment with KYPROLIS. KYPROLIS can cause increased serum transaminases. Monitor liver enzymes regularly regardless of baseline values. Reduce or withhold dose as appropriate.

Thrombotic Microangiopathy

- Cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), including fatal outcome have occurred in patients receiving KYPROLIS. Monitor for signs and symptoms of TTP/HUS. Discontinue KYPROLIS if diagnosis is suspected. If the diagnosis of TTP/HUS is excluded, KYPROLIS may be restarted. The safety of reinitiating KYPROLIS therapy in patients previously experiencing TTP/HUS is not known.

Posterior Reversible Encephalopathy Syndrome (PRES)

- Cases of PRES have occurred in patients receiving KYPROLIS. PRES was formerly known as Reversible Posterior Leukoencephalopathy Syndrome. Consider a neuro-radiological imaging (MRI) for onset of visual or neurological symptoms. Discontinue KYPROLIS if PRES is suspected and evaluate. The safety of reinitiating KYPROLIS therapy in patients previously experiencing PRES is not known.

Embryo-fetal Toxicity

- KYPROLIS can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals.
- Females of reproductive potential should be advised to avoid becoming pregnant while being treated with KYPROLIS. Males of reproductive potential should be advised to avoid fathering a child while being treated with KYPROLIS. If this drug is used during pregnancy, or if pregnancy occurs while taking this drug, the patient should be apprised of the potential hazard to the fetus.

ADVERSE REACTIONS

- The most common adverse reactions occurring in at least 20% of patients treated with KYPROLIS in the combination therapy trials: anemia, neutropenia, diarrhea, dyspnea, fatigue, thrombocytopenia, pyrexia, insomnia, muscle spasm, cough, upper respiratory tract infection, hypokalemia.

The most common adverse reactions occurring in at least 20% of patients treated with KYPROLIS in monotherapy trials: anemia, fatigue, thrombocytopenia, nausea, pyrexia, dyspnea, diarrhea, headache, cough, edema peripheral.

Full prescribing information for the U.S. is available at www.kyprolis.com.

About Amgen

Amgen is committed to unlocking the potential of biology for patients suffering from serious illnesses by discovering, developing, manufacturing and delivering innovative human therapeutics. This approach begins by using tools like advanced human genetics to unravel the complexities of disease and understand the fundamentals of human biology.

Amgen focuses on areas of high unmet medical need and leverages its expertise to strive for solutions that improve health outcomes and dramatically improve people's lives. A biotechnology pioneer since 1980, Amgen has grown to be one of the world's leading independent biotechnology companies, has reached millions of patients around the world and is developing a pipeline of medicines with breakaway potential.

For more information, visit www.amgen.com and follow us on www.twitter.com/amgen.

Forward Looking Statements

This news release contains forward-looking statements that are based on the current expectations and beliefs of Amgen. All statements, other than statements of historical fact, are statements that could be deemed forward-looking statements, including estimates of revenues, operating margins, capital expenditures, cash, other financial metrics, expected legal, arbitration, political, regulatory or clinical results or practices, customer and prescriber patterns or practices, reimbursement activities and outcomes and other such estimates and results. Forward-looking statements involve significant risks and uncertainties, including those discussed below and more fully described in the Securities and Exchange Commission reports filed by Amgen, including our most recent annual report on Form 10-K and any subsequent periodic reports on Form 10-Q and Form 8-K. Unless otherwise noted, Amgen is providing this information as of the date of this news release and does not undertake any obligation to update any forward-looking statements contained in this document as a result of new information, future events or otherwise.

No forward-looking statement can be guaranteed and actual results may differ materially from those we project. Discovery or identification of new product candidates or development of new indications for existing products cannot be guaranteed and movement from concept to product is uncertain; consequently, there can be no guarantee that any particular product candidate or development of a new indication for an existing product will be successful and become a commercial product. Further, preclinical results do not guarantee safe and effective performance of product candidates in humans. The complexity of the human body cannot be perfectly, or sometimes, even adequately modeled by computer or cell culture systems or animal models. The length of time that it takes for us to complete clinical trials and obtain regulatory approval for product marketing has in the past varied and we expect similar variability in the future. Even when clinical trials are successful, regulatory authorities may question the sufficiency for approval of the trial endpoints we have selected. We develop product candidates internally and through licensing collaborations, partnerships and joint ventures. Product candidates that are derived from relationships may be subject to disputes between the parties or may prove to be not as effective or as safe as we may have believed at the time of entering into such relationship. Also, we or others could identify safety, side effects or manufacturing problems with our products after they are on the market.

Our results may be affected by our ability to successfully market both new and existing products domestically and internationally, clinical and regulatory developments involving current and future products, sales growth of recently launched products, competition from other products including biosimilars, difficulties or delays in manufacturing our products and global economic conditions. In addition, sales of our products are affected by pricing pressure, political and public scrutiny and reimbursement policies imposed by third-party payers, including governments, private insurance plans and managed care providers and may be affected by regulatory, clinical and guideline developments and domestic and international trends toward managed care and healthcare cost containment. Furthermore, our research, testing, pricing, marketing and other operations are subject to extensive regulation by domestic and foreign government regulatory authorities. We or others could identify safety, side effects or manufacturing problems with our products after they are on the market. Our business may be impacted by government investigations, litigation and product liability claims. In addition, our business may be impacted by the adoption of new tax legislation or exposure to additional tax liabilities. If we fail to meet the compliance obligations in the corporate integrity agreement between us and the U.S. government, we could become subject to significant sanctions. Further, while we routinely obtain patents for our products and technology, the protection offered by our patents and patent applications may be challenged, invalidated or circumvented by our competitors, or we may fail to prevail in present and future intellectual property litigation. We perform a substantial amount of our commercial manufacturing activities at a few key facilities and also depend on third parties for a portion of our manufacturing activities, and limits on supply may constrain sales of certain of our current products and product candidate development. In addition, we compete with other companies with respect to many of our marketed products as well as for the discovery and development of new products. Further, some raw materials, medical devices and component parts for our products are supplied by sole third-party suppliers. The discovery of significant problems with a product similar to one of our products that implicate an entire class of products could have a material adverse effect on sales of the affected products

and on our business and results of operations. Our efforts to acquire other companies or products and to integrate the operations of companies we have acquired may not be successful. We may not be able to access the capital and credit markets on terms that are favorable to us, or at all. We are increasingly dependent on information technology systems, infrastructure and data security. Our stock price is volatile and may be affected by a number of events. Our business performance could affect or limit the ability of our Board of Directors to declare a dividend or our ability to pay a dividend or repurchase our common stock.

The scientific information discussed in this news release relating to new indications for our products is preliminary and investigative and is not part of the labeling approved by the U.S. Food and Drug Administration or the European Medicines Agency for the products. The products are not approved for the investigational use(s) discussed in this news release, and no conclusions can or should be drawn regarding the safety or effectiveness of the products for these uses.

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