FDA Approves New Kyprolis® (Carfilzomib) Combination Therapy For The Treatment Of Patients With Relapsed Or Refractory Multiple Myeloma

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Pivotal Head-To-Head ENDEAVOR Study Shows Kyprolis and Dexamethasone Doubled Progression-Free Survival Versus Velcade® (Bortezomib) and Dexamethasone

Kyprolis Label Expansion Represents Critical Advancement for Patients With Relapsed or Refractory Multiple Myeloma, Offering New Option For Backbone Therapy

Approval Expands Kyprolis Indication and Converts Monotherapy Indication to Full Approval

THOUSAND OAKS, Calif., Jan. 21, 2016 /PRNewswire/ -- Amgen (NASDAQ: AMGN) today announced that the U.S. Food and Drug Administration (FDA) has approved the supplemental New Drug Application (sNDA) of Kyprolis® (carfilzomib) for Injection 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. The FDA also approved Kyprolis as a single agent for the treatment of patients with relapsed or refractory multiple myeloma who have received one or more lines of therapy. This FDA decision converts to full approval the initial accelerated approval Kyprolis received in July 2012 as a single agent.

Experience the interactive Multimedia News Release here: http://www.multivu.com/players/English/74140510-kyprolis-endeavor-expanded-approval/.

"Kyprolis is the only approved therapy for relapsed multiple myeloma with proven efficacy as a single agent, doublet and triplet combination that is offered in a variety of doses to meet individual patient needs," said Sean E. Harper, M.D., executive vice president of Research and Development at Amgen. "Importantly, this new approval supports the use of Kyprolis as a backbone therapy for the management of relapsed multiple myeloma, a difficult-to-treat blood cancer."

"Multiple myeloma remains an incurable disease where relapse inevitably occurs and over time patients become resistant to treatments," said Dr. Ruben Niesvizky, director of the Multiple Myeloma Center at Weill Cornell Medicine and New York-Presbyterian/Weill Cornell Medical Center. "As a clinician, I'm pleased with the tremendous progress that we have seen in the past 12 months in multiple myeloma treatment. This FDA approval is important because it provides physicians with flexible options for Kyprolis use in helping to manage this challenging disease."

The approval is based on results from the Phase 3 head-to-head ENDEAVOR study. This was a superiority trial in which the primary endpoint was progression-free survival (PFS). The data showed patients with relapsed multiple myeloma treated with Kyprolis and dexamethasone achieved 50 percent greater PFS of 18.7 months compared to 9.4 months in those receiving Velcade® (bortezomib) and dexamethasone (HR=0.53; 95 percent CI: 044, 0.65 *p*<0.0001), a current standard of care in relapsed multiple myeloma. Patients in the study were treated until disease progression. The most common adverse reactions (greater than or equal to 20 percent) in the Kyprolis arm were anemia, diarrhea, dyspnea, fatigue, insomnia, pyrexia and thrombocytopenia.

This new indication for Kyprolis is the second in six months. In July 2015, the FDA approved another expanded indication for Kyprolis in combination with lenalidomide and dexamethasone (KRd) for the treatment of patients with multiple myeloma who have received one to three prior lines of therapy.

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.[2-4] In the U.S., there are nearly 90,000 people living with, or in remission from, multiple myeloma.[5] Approximately, 26,850 Americans are diagnosed with multiple myeloma each year and 11,240 patient deaths are reported on an annual basis.[5]

About ENDEAVOR

The randomized ENDEAVOR (RandomizEd, OpeN Label, Phase 3 Study of Carfilzomib Plus DExamethAsone Vs Bortezomib Plus DexamethasOne in Patients With Relapsed Multiple Myeloma) trial of 929 patients evaluated Kyprolis in combination with low-dose dexamethasone (Kd), versus 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, 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 all pre-specified subgroups, including bortezomib-naïve patients, those with high- or standard-risk cytogenetics and with or without prior transplantation.

Kd also demonstrated improvement over Vd for secondary endpoints, achieving a higher overall response rate (77 percent vs. 63 percent; *p*<0.0001) and lower rate of grade 2 or higher neuropathy events (6 percent [95 percent CI: 4, 8] vs. 32 percent [95 percent CI: 28, 36]). 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), and 12.5 percent and 6.2 percent of patients achieved a complete 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. 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).

Rates of grade 3 or higher adverse events were 73 percent in the Kyprolis group and 67 percent in the bortezomib group. 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).

Patients received treatment until progression with Kyprolis as a 30-minute infusion on days 1, 2, 8, 9, 15 and 16 of 28 day treatment cycles, along with low-dose dexamethasone (20 mg). 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.[7] 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] The irreversibility of Kyprolis' binding has also been shown to offer a more sustained inhibition of the targeted enzymes.[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 and the European Union. Additional regulatory applications for Kyprolis are underway and have been submitted to health authorities worldwide.

Kyprolis is a product of Onyx Pharmaceuticals, Inc. Onyx Pharmaceuticals is a subsidiary of Amgen and holds development and commercialization rights to Kyprolis globally, excluding Japan.

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

Patient Support Program

Amgen is proud to offer Onyx Pharmaceuticals 360® (Onyx 360) which is a patient support program designed to provide personalized services to patients living with cancer. Upon enrollment, patients are paired with a dedicated Onyx 360 Oncology Nurse Ambassador who is trained to help navigate their treatment journey and address daily and long term concerns. Onyx 360 also provides access to a network of resources and third-party services including transportation, emotional support and financial and product reimbursement assistance. Onyx 360 services are provided to patients at no cost. For more information, please visit www.kyprolis.com/support-during-treatment.

Editor's Note: Dr. Niesvizky is an advisory board member for and paid consultant to Onyx Pharmaceuticals, Inc.

Important Safety Information Regarding Kyprolis® (carfilzomib) for Injection

INDICATION(S)

- KYPROLIS® (carfilzomib) is indicated 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.
- KYPROLIS® (carfilzomib) is indicated as a single agent for the treatment of patients with relapsed or refractory multiple myeloma who have received one or more lines of therapy.

IMPORTANT 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 $\geq$ 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 neuroradiological 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 events 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 events occurring in at least 20% of patients treated with KYPROLIS in monotherapy trials: anemia, fatigue, thrombocytopenia, nausea, pyrexia, dyspnea, diarrhea, headache, cough, edema peripheral.

Please see full Prescribing Information 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 biologics manufacturing 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 Inc. and its subsidiaries (Amgen, we or us) and are subject to a number of risks, uncertainties and assumptions that could cause actual results to differ materially from those described. 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 (SEC) reports filed by Amgen Inc., including Amgen Inc.'s most recent annual report on Form 10-K and any subsequent periodic reports on Form 10-Q and Form 8-K. Please refer to Amgen Inc.'s most recent Forms 10-K, 10-Q and 8-K for additional information on the uncertainties and risk factors related to our business. Unless otherwise noted, Amgen is providing this information as of Jan. 21, 2016, and expressly disclaims any duty to update information contained in this news release.

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 and our partners to complete clinical trials and obtain regulatory approval for product marketing has in the past varied and we expect similar variability in the future. 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 business may be impacted by government investigations, litigation and product liability claims. 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. We depend on third parties for a significant portion of our manufacturing capacity for the supply of certain of our current and future products and limits on supply may constrain sales of certain of our current products and product candidate development.

In addition, sales of our products (including products of our wholly-owned subsidiaries) are affected by the 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 as well as U.S. legislation affecting pharmaceutical pricing and reimbursement. Government and others' regulations and reimbursement policies may affect the development, usage and pricing of our products. In addition, we compete with other companies with respect to some of our marketed products as well as for the discovery and development of new products. We believe that some of our newer products, product candidates or new indications for existing products, may face competition when and as they are approved and marketed. Our products may compete against products that have lower prices, established reimbursement, superior performance, are easier to administer, or that are otherwise competitive with our products. In addition, while we and our partners routinely obtain patents for our and their products and technology, the protection of our products offered by patents and patent applications may be challenged, invalidated or circumvented by our or our partners' competitors and there can be no guarantee of our or our partners' ability to obtain or maintain patent protection for our products or product candidates. We cannot guarantee that we will be able to produce commercially successful products or maintain the commercial success of our existing products. Our stock price may be affected by actual or perceived market opportunity, competitive position, and success or failure of our products or product candidates. Further, 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 integrate the operations of companies we have acquired may not be successful. We may experience difficulties, delays or unexpected costs and not achieve anticipated benefits and savings from our ongoing restructuring plan. 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 common stock.

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