



## Amgen Submits Applications In The US And Europe For Kyprolis® (carfilzomib) For The Treatment Of Relapsed Multiple Myeloma

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### US Submission Designed to Support Conversion From Accelerated to Full FDA Approval and Expansion of Current Approved Indication

### EMA Grants Kyprolis Accelerated Assessment and Orphan Drug Designation

THOUSAND OAKS, Calif. and SOUTH SAN FRANCISCO, Calif., Jan. 27, 2015 /PRNewswire/ -- Amgen (NASDAQ:AMGN) and its subsidiary Onyx Pharmaceuticals, Inc., today announced the submission of a supplemental New Drug Application (sNDA) to the U.S. Food and Drug Administration (FDA) and a Marketing Authorization Application (MAA) to the European Medicines Agency (EMA) for Kyprolis® (carfilzomib) for Injection to seek approval for the treatment of patients with relapsed multiple myeloma who have received at least one prior therapy. In the U.S., the sNDA is designed to support the conversion of accelerated approval to full approval and expand the current approved indication. In the European Union (EU), Kyprolis received orphan drug designation and the MAA has been granted accelerated assessment.

The sNDA and MAA are based on data from the Phase 3 ASPIRE (CArfilzomib, Lenalidomide, and DexamethaSone versus Lenalidomide and Dexamethasone for the treatment of PatIents with Relapsed Multiple MyEloma) trial and other relevant data.

"Multiple myeloma is an incurable blood cancer that often becomes resistant to treatment, underscoring the need for new therapeutic options that provide deep and durable responses to extend the time patients live without their disease progressing," said Pablo J. Cagnoni, M.D., president, Onyx Pharmaceuticals, Inc. "The U.S. and EU submissions support our goal of bringing Kyprolis to patients with relapsed multiple myeloma."

Orphan designation is granted by the EMA for medicines intended for the treatment, prevention or diagnosis of a disease that is life threatening and has a prevalence in the EU of no more than five in 10,000. The intended medicine must aim to provide significant benefit to those affected by the condition.<sup>1</sup>

Kyprolis is in a class of drugs called proteasome inhibitors and was granted accelerated approval by the FDA in 2012. Kyprolis is also approved for use in Argentina, Israel and Mexico.

#### About Multiple Myeloma

Multiple myeloma is the second most common hematologic cancer and results from an abnormality of plasma cells, usually in the bone marrow. Worldwide, nearly 230,000 people are living with multiple myeloma.<sup>2</sup> In 2012, approximately 114,000 new cases were diagnosed and 80,000 people died.<sup>3</sup> In the U.S., approximately 83,000 people were living with multiple myeloma in 2011. The estimated number of new cases in 2014 was 24,000 and the estimated number of deaths was 11,000.<sup>4</sup> In Europe, approximately 89,000 people are living with multiple myeloma.<sup>2</sup> Approximately 39,000 new cases were diagnosed and 24,000 people died in 2012.<sup>2</sup>

#### About ASPIRE

The international, randomized Phase 3 ASPIRE (CArfilzomib, Lenalidomide, and DexamethaSone versus Lenalidomide and Dexamethasone for the treatment of PatIents with Relapsed Multiple MyEloma) trial evaluated Kyprolis in combination with lenalidomide and low-dose dexamethasone, versus lenalidomide and low-dose dexamethasone alone, in patients with relapsed multiple myeloma following treatment with one to three prior regimens. The primary endpoint of the trial was progression-free survival, defined as the time from treatment initiation to disease progression or death. Secondary endpoints included overall survival, overall response rate, duration of response, disease control rate, health-related quality of life and safety. Patients were randomized to receive Kyprolis (20 mg/m<sup>2</sup> on days 1 and 2 of cycle 1 only, escalating to 27 mg/m<sup>2</sup> on days 8, 9, 15 and 16 of cycle 1 and continuing on days 1, 2, 8, 9, 15 and 16 of subsequent cycles), in addition to a standard dosing schedule of lenalidomide (25 mg per day for 21 days on, 7 days off) and low-dose dexamethasone (40 mg per week in 4 week cycles), versus lenalidomide and low-dose dexamethasone alone. The study randomized 792 patients at sites in North America, Europe and Israel.

Onyx Pharmaceuticals conducted the ASPIRE trial under a Special Protocol Assessment (SPA) from the FDA and received Scientific Advice from the EMA on the design and planned analysis of the study.

#### About Kyprolis® (carfilzomib) for Injection

On July 20, 2012, the U.S. FDA granted accelerated approval of Kyprolis® (carfilzomib) for Injection for the treatment of patients with multiple myeloma who have received at least two prior therapies including bortezomib and an immunomodulatory agent (IMiD) and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval was based on response rate. Clinical benefit, such as improvement in survival or symptoms, has not been verified.

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 about Kyprolis, visit [www.kyprolis.com](http://www.kyprolis.com).

#### Important Safety Information Regarding Kyprolis® (carfilzomib) for Injection

This safety information is specific to the current U.S. approved indication, which is based on Phase 2 studies.

Safety data have been evaluated in 526 patients with relapsed and/or refractory multiple myeloma who received single-agent Kyprolis. There were 37 deaths in the Phase 2 studies, or 7 percent of patients. The most common causes of death, other than disease progression, were cardiac events (5 patients), end-organ failure (4 patients) and infection (4 patients). Important warnings and precautions include cardiac arrest, congestive heart failure, myocardial ischemia, pulmonary hypertension, pulmonary complications, infusion reactions, tumor lysis syndrome, thrombocytopenia, hepatic toxicity and embryo-fetal toxicity.

Death due to cardiac arrest has occurred within a day of Kyprolis administration. Patients with New York Heart Association Class III and IV heart failure, myocardial infarction in the preceding 6 months and conduction abnormalities uncontrolled by medications were not eligible for the clinical trials. These patients may be at greater risk for cardiac complications.

Pulmonary arterial hypertension (PAH) was reported in 2 percent of patients treated with Kyprolis and was Grade 3 or greater in less than 1 percent of patients. Dyspnea was reported in 35 percent of patients enrolled in clinical trials. Grade 3 dyspnea occurred in 5 percent; no Grade 4 events and 1 death (Grade 5) was reported.

Infusion reactions, characterized by a spectrum of systemic symptoms including fever, chills, arthralgia, myalgia, facial flushing, facial edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina can occur immediately following or up to 24 hours after administration of Kyprolis. Administration of dexamethasone prior to Kyprolis reduces the incidence and severity of reactions. Tumor lysis syndrome (TLS) occurred following Kyprolis administration in <1 percent of patients. Patients with multiple myeloma and a high tumor burden should be considered to be at greater risk for TLS.

Thrombocytopenia following Kyprolis administration resulted in a dose reduction in 1 percent of patients and discontinuation of treatment with Kyprolis in <1 percent of patients.

Cases of hepatic failure, including fatal cases, have been reported (<1 percent). Kyprolis can cause elevations of serum transaminases and bilirubin.

There are no adequate and well-controlled studies in pregnant women using Kyprolis. Females of reproductive potential should be advised to avoid becoming pregnant while being treated with Kyprolis.

The most common serious adverse reactions were pneumonia, acute renal failure, pyrexia and congestive heart failure. The most common adverse reactions (incidence of 30 percent or greater) observed in clinical trials of patients with multiple myeloma were fatigue, anemia, nausea, thrombocytopenia, dyspnea, diarrhea and pyrexia. Serious adverse reactions were reported in 45 percent of patients.

Full prescribing information is available at [www.kyprolis.com](http://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](http://www.amgen.com) and follow us on [www.twitter.com/amgen](https://www.twitter.com/amgen).

#### **About Onyx Pharmaceuticals, Inc.**

Based in South San Francisco, California, Onyx Pharmaceuticals, Inc., an Amgen subsidiary, is a global biopharmaceutical company engaged in the development and commercialization of innovative therapies for improving the lives of people with cancer. The company is focused on developing novel medicines that target key molecular pathways. For more information about Onyx, visit the company's website at [www.onyx.com](http://www.onyx.com). Onyx Pharmaceuticals is on Twitter. Sign up to follow our Twitter feed @OnyxPharm at <http://twitter.com/OnyxPharm>.

#### **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) 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 Amgen's business. Unless otherwise noted, Amgen is providing this information as of Jan. 27, 2015 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 Amgen projects. 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 Amgen and its partners to complete clinical trials and obtain regulatory approval for product marketing has in the past varied and Amgen expects similar variability in the future. Amgen develops 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 Amgen may have believed at the time of entering into such relationship. Also, Amgen or others could identify safety, side effects or manufacturing problems with Amgen's products after they are on the market. Amgen's business may be impacted by government investigations, litigation and product liability claims. If Amgen fails to meet the compliance obligations in the corporate integrity agreement between Amgen and the U.S. government, Amgen could become subject to significant sanctions. Amgen depends on third parties for a significant portion of its manufacturing capacity for the supply of certain of its current and future products and limits on supply may constrain sales of certain of its current products and product candidate development.

In addition, sales of Amgen's products (including products of Amgen's 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 Amgen's products. In addition, Amgen competes with other companies with respect to some of its marketed products as well as for the discovery and development of new products. Amgen believes that some of its newer products, product candidates or new indications for existing products, may face competition when and as they are approved and marketed. Amgen's products may compete against products that have lower prices, established reimbursement, superior performance, are easier to administer, or that are otherwise competitive with its products. In addition, while Amgen and its partners routinely obtain patents for their products and technology, the protection of Amgen's products offered by patents and patent applications may be challenged, invalidated or circumvented by its competitors and there can be no guarantee of Amgen's or its partners' ability to obtain or maintain patent protection for Amgen's products or product candidates. Amgen cannot guarantee that it will be able to produce commercially successful products or maintain the commercial success of its existing products. Amgen's stock price may be affected by actual or perceived market opportunity, competitive position and success or failure of its products or product candidates. Further, the discovery of significant problems with a product similar to one of Amgen's products that implicate an entire class of products could have a material adverse effect on sales of the affected products and on Amgen's business and results of operations. Amgen's efforts to integrate the operations of companies it has acquired may not be successful. Cost saving initiatives may result in Amgen incurring impairment or other related charges on its assets. Amgen may experience difficulties, delays or unexpected costs and not achieve anticipated cost savings from its recently announced restructuring plans. Amgen's business performance could affect or limit the ability of Amgen's Board of Directors to declare a dividend or their ability to pay a dividend or repurchase Amgen common stock.

The scientific information discussed in this news release relating to new indications for Amgen's products is preliminary and investigative and is not part of the labeling approved by the U.S. Food and Drug Administration (FDA) 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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<sup>1</sup> European Medicines Agency. Orphan Designation Page. [http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/\\_general\\_content\\_000029.jsp](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/_general_content_000029.jsp)

<sup>2</sup> Bray F, Ren JS, Masuyer E, Ferlay J. Estimates of global cancer prevalence for 27 sites in the adult population in 2008. *Int J Cancer*. 2013 Mar. 1;132(5):1133-45. doi: 10.1002/ijc.27711. Epub 2012 Jul 26.

<sup>3</sup> Ferlay J, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>, accessed on 15/January/2015.

<sup>4</sup> National Cancer Institute. SEER Stat Fact Sheets: Myeloma. <http://seer.cancer.gov/statfacts/html/mulmy.html>.



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