



Amgen Submits Supplemental New Drug Application For KYPROLIS® (carfilzomib) Once-Weekly 70 mg/m² In Combination With Dexamethasone

August 27, 2018

Filing Based on Data From Phase 3 Head-to-Head A.R.R.O.W. Study

THOUSAND OAKS, Calif., Aug. 27, 2018 /PRNewswire/ -- Amgen (NASDAQ:AMGN) today announced the submission of a supplemental New Drug Application (sNDA) to the U.S. Food and Drug Administration (FDA) to expand the Prescribing Information for KYPROLIS® (carfilzomib) to include a once-weekly dosing option in combination with dexamethasone (Kd) for patients with relapsed or refractory multiple myeloma. The sNDA is based on data from the Phase 3 A.R.R.O.W. trial, demonstrating KYPROLIS administered once-weekly at 70 mg/m² with dexamethasone (once-weekly Kd) achieved superior progression-free survival (PFS) and overall response rates (ORR), with a comparable safety profile versus the twice-weekly KYPROLIS at 27 mg/m² and dexamethasone (twice-weekly Kd).

The FDA is reviewing the application under the Oncology Center of Excellence Real-Time Oncology Review and Assessment Aid pilot programs, which aim to explore a more efficient review process to ensure that safe and effective treatments are available to patients as early as possible.

"I'm proud of our continued dedication to the KYPROLIS clinical program, with a focus on generating additional data to reduce the dosing and administration burden on patients with relapsed or refractory multiple myeloma," said David M. Reese, M.D., executive vice president of Research and Development at Amgen. "Data from the Phase 3 A.R.R.O.W. study illustrates KYPROLIS' potential to extend the time patients live without their disease progressing while also providing a more convenient once-weekly dosing option for this frequently relapsing and difficult-to-treat cancer. We look forward to working with the Agency to bring this more streamlined dosing regimen to patients."

A.R.R.O.W. included 478 patients with relapsed and refractory multiple myeloma who received two or three prior lines of therapy, including a proteasome inhibitor and an immunomodulatory agent. Patients treated with once-weekly Kd achieved a statistically significant 3.6 month improvement in PFS compared to the twice-weekly regimen (median PFS 11.2 months for once-weekly Kd versus 7.6 months for twice-weekly Kd; HR=0.69; 95 percent CI: 0.54-0.88; one-sided $p=0.0014$). The ORR in patients treated with once-weekly Kd was 62.9 percent versus 40.8 percent for those treated with the twice-weekly regimen ($p<0.0001$). In addition, 7.1 percent had complete responses or better in the once-weekly arm versus 1.7 percent in the twice-weekly arm in this refractory patient population. The interim data were presented during an oral session at the 54th Annual Meeting of the American Society of Clinical Oncology and simultaneously published in *The Lancet Oncology*.

The overall safety profiles of the two arms were comparable, with no new safety risks identified in the once-weekly arm. The most frequently reported treatment-emergent adverse events (greater than or equal to 20 percent) in either treatment arm were anemia, diarrhea, fatigue, hypertension, insomnia and pyrexia.

About A.R.R.O.W.

The A.R.R.O.W. (RAndomized, Open-label, Phase 3 Study in Subjects with RElapsed and Refractory Multiple Myeloma Receiving Carfilzomib in Combination with Dexamethasone, Comparing OOnce-Weekly versus Twice-weekly Carfilzomib Dosing) trial evaluated 478 patients with relapsed and refractory multiple myeloma who have received at least two but no more than three prior therapies, including bortezomib and an immunomodulatory drug. Those included in the study were randomized to receive a 30-minute infusion of once-weekly KYPROLIS (20 mg/m² on day 1 of cycle 1; 70 mg/m² on days 8 and 15 of cycle 1; and 70 mg/m² on days 1, 8 and 15 of subsequent cycles) with dexamethasone (40 mg) versus a 10-minute infusion of twice-weekly KYPROLIS (20 mg/m² on days 1 and 2 of cycle 1; 27 mg/m² on days 8, 9, 15 and 16 of cycle 1; and 27 mg/m² on days 1, 2, 8, 9, 15 and 16 of subsequent cycles) with dexamethasone (40 mg). The primary endpoint of the trial was PFS, defined as the time from randomization to disease progression or death. Secondary endpoints included ORR, overall survival, and safety and tolerability.

The trial was conducted in approximately 100 sites worldwide. For more information about this trial, please visit www.clinicaltrials.gov under trial identification number NCT02412878.

About Multiple Myeloma

Multiple myeloma is an incurable blood cancer, characterized by a recurring pattern of remission and relapse.¹ It is a rare and life-threatening disease that accounts for approximately one percent of all cancers.^{2,3} Worldwide, approximately 114,000 people are diagnosed with multiple myeloma each year and 80,000 patient deaths are reported on an annual basis.²

About KYPROLIS® (carfilzomib)

Proteasomes play an important role in cell function and growth by breaking down proteins that are damaged or no longer needed.⁴ KYPROLIS has been shown to block proteasomes, leading to an excessive build-up of proteins within cells.⁵ 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.^{4,5}

Since its first approval in 2012, approximately 80,000 patients worldwide have received KYPROLIS. 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, Australia, Bahrain, Canada, Hong Kong, Israel, Japan, Kuwait, Lebanon, Macao, Mexico, Thailand, Colombia, S. Korea, Canada, Qatar, Switzerland, United Arab Emirates, Turkey, Russia, Brazil, India, Oman and the U.S. Additional regulatory

applications for KYPROLIS are underway and have been submitted to health authorities worldwide.

Important U.S. KYPROLIS® (carfilzomib) 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 administration.
- Monitor patients for signs or symptoms of cardiac failure or 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 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.
- For 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 prior to starting treatment with KYPROLIS and remain under close follow-up with fluid management.

Acute Renal Failure

- Cases of acute renal failure, including some fatal renal failure events, and renal insufficiency adverse events (including renal failure) have occurred. 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. Patients with 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, and withhold until 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. Some events have been fatal. In the event of drug-induced pulmonary toxicity, discontinue KYPROLIS.

Pulmonary Hypertension

- Pulmonary arterial hypertension (PAH) was reported. 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 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 based on a benefit/risk assessment.

Hypertension

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

Venous Thrombosis

- Venous thromboembolic events (including deep venous thrombosis and pulmonary embolism) have been observed. 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 hormonal contraception associated with a risk of thrombosis should consider an alternative method of effective contraception during treatment.

Infusion Reactions

- Infusion reactions, including life-threatening reactions, have occurred. 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. Premedicate with dexamethasone to reduce the incidence and severity of infusion reactions. Inform patients of the risk and of symptoms and seek immediate medical attention if they occur.

Hemorrhage

- Fatal or serious cases of hemorrhage have been reported. Hemorrhagic events have included gastrointestinal, pulmonary, and intracranial hemorrhage and epistaxis. Promptly evaluate signs and symptoms of blood loss. Reduce or withhold dose as appropriate.

Thrombocytopenia

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

Hepatic Toxicity and Hepatic Failure

- Cases of hepatic failure, including fatal cases, have occurred. 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. Monitor for signs and symptoms of TTP/HUS. Discontinue if diagnosis is suspected. If the diagnosis of TTP/HUS is excluded, KYPROLIS may be restarted. The safety of reinitiating KYPROLIS is not known.

Posterior Reversible Encephalopathy Syndrome (PRES)

- Cases of PRES have occurred in patients receiving KYPROLIS. If PRES is suspected, discontinue and evaluate with appropriate imaging. The safety of reinitiating KYPROLIS is not known.

Increased Fatal and Serious Toxicities in Combination with Melphalan and Prednisone in Newly Diagnosed Transplant-ineligible Patients

- In a clinical trial of transplant-ineligible patients with newly diagnosed multiple myeloma comparing KYPROLIS, melphalan, and prednisone (KMP) vs bortezomib, melphalan, and prednisone (VMP), a higher incidence of serious and fatal adverse events was observed in patients in the KMP arm. KMP is not indicated for transplant-ineligible patients with newly diagnosed multiple myeloma.

Embryo-fetal Toxicity

- KYPROLIS can cause fetal harm when administered to a pregnant woman.
- 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 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 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's Commitment to Oncology

Amgen Oncology is committed to helping patients take on some of the toughest cancers, such as those that have been resistant to drugs, those that

progress rapidly through the body and those where limited treatment options exist. Amgen's supportive care treatments help patients combat certain side effects of strong chemotherapy, and our targeted medicines and immunotherapies focus on more than a dozen different malignancies, ranging from blood cancers to solid tumors. With decades of experience providing therapies for cancer patients, Amgen continues to grow its portfolio of innovative and biosimilar oncology medicines.

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 current reports on 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, including our devices, 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. 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, including in Puerto Rico, 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. Certain of our distributors, customers and payers have substantial purchasing leverage in their dealings with us. 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. A breakdown, cyberattack or information security breach could compromise the confidentiality, integrity and availability of our systems and our data. 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. We may not be able to access the capital and credit markets on terms that are favorable to us, or at all.

CONTACT:

Amgen, Thousand Oaks
Kristen Davis, 805-447-3008 (Media)
Andrea Fassacesia, 805-905-2575 (Media)
Arvind Sood, 805-447-1060 (Investors)

References

1. Jakubowiak A. Management Strategies for Relapsed/Refractory Multiple Myeloma: Current Clinical Perspectives. *Seminars in Hematology*. 2012; 49(3)(1),S16-S32.
2. GLOBOCAN 2012. Global Prevalence and Incidence. Available at: http://globocan.iarc.fr/old/summary_table_pop_prev.asp?selection=224900&title=World&sex=0&window=1&sort=0&submit=%C2%A0Execute

%C2%A0http://globocan.iarc.fr/old/summary_table_pop_prev.asp?selection=224900&title=World&sex=0&window=1&sort=0&submit=%C2%A0Execute%C2%A0. Accessed on April 19, 2018.

3. American Cancer Society. About Multiple Myeloma. Available at <https://www.cancer.org/content/dam/CRC/PDF/Public/8738.00.pdf>. Accessed on April 19, 2018.
4. Moreau P, Richardson PG, Cavo M, et al. Proteasome Inhibitors in Multiple Myeloma: 10 Years Later. *Blood*. 2012; 120(5):947-959.
5. Kortuem KM and Stewart AK. Carfilzomib. *Blood*. 2012; 121(6):893-897.



 View original content with multimedia: <http://www.prnewswire.com/news-releases/amgen-submits-supplemental-new-drug-application-for-kyprolis-carfilzomib-once-weekly-70-mgm2-in-combination-with-dexamethasone-300702500.html>

SOURCE Amgen