



**Approved on July 24, 2015,** Kyprolis<sup>®</sup> (carfilzomib) for Injection is a prescription medication used in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior lines of therapy.<sup>1</sup>

## INDICATION

Kyprolis is a proteasome inhibitor that is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior lines of therapy.<sup>1</sup>

## HOW KYPROLIS WORKS

Proteasomes play an important role in cell function and growth by breaking down proteins that are damaged or no longer needed. Multiple myeloma cells produce certain proteins, such as serum or urine M proteins.<sup>2</sup> Kyprolis blocks proteasomes, which can lead to an excessive build-up of proteins within cells. In some cells, Kyprolis can cause cell death, especially in cancer cells because they are more likely to contain a higher amount of abnormal proteins.<sup>3</sup>

## DOSING AND ADMINISTRATION

Kyprolis is administered intravenously as a 10 minute infusion on two consecutive days each week for three weeks, followed by a 12 day rest period.<sup>1</sup> Each 28-day period is considered one treatment cycle.<sup>3</sup>

In combination with lenalidomide and dexamethasone, for patients who have received one to three prior lines of therapy, Kyprolis is administered at a starting dose of 20 mg/m<sup>2</sup>/day in Cycle 1 on Days 1 and 2. If tolerated, the dose should be escalated to a target dose of 27 mg/m<sup>2</sup>/day on Day 8 of Cycle 1 and in subsequent cycles. Kyprolis is omitted on Days 8 and 9 during cycles 13-18.<sup>1</sup>

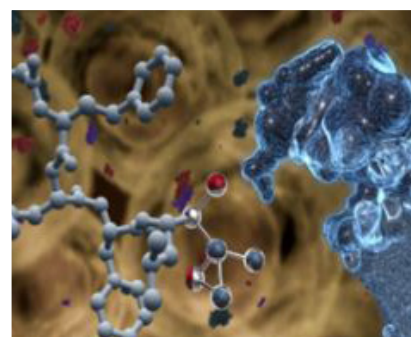
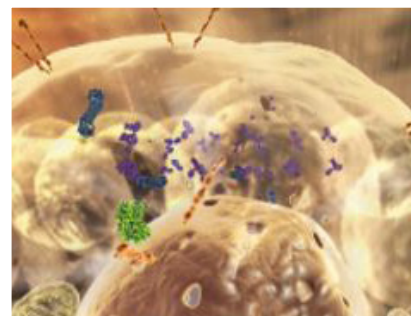
## PIVOTAL STUDY RESULTS

The U.S. Food and Drug Administration (FDA) approval of Kyprolis is based on the Phase 3 ASPIRE trial.<sup>1</sup>

**ASPIRE** was an international, randomized trial which evaluated Kyprolis in combination with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone, in patients following treatment with one to three prior regimens.<sup>4</sup> In the study:

- In the Kyprolis arm, patients lived significantly longer without their disease worsening compared to those in the control (median progression-free survival [PFS], 26.3 vs. 17.6 months, respectively [HR=0.69; 95 percent CI: 0.57-0.83; p<0.0001]).<sup>4</sup>
- Patients treated with the Kyprolis combination were three times more likely to be disease free compared to those in the control (31.8 vs. 9.3 percent of patients, respectively, achieved a complete response or better).<sup>4</sup>
- While the data for overall survival, a secondary endpoint, are not yet mature, the analysis showed a trend in favor of the Kyprolis combination compared with the control.<sup>4</sup>
- The safety profile of Kyprolis observed in ASPIRE was consistent with previous studies, including the rate of cardiac events. Treatment discontinuation due to adverse events and on-study deaths were comparable between the two arms.<sup>4</sup>

Information about Amgen clinical trials for Kyprolis can be obtained by healthcare professionals or at [www.clinicaltrials.gov](http://www.clinicaltrials.gov)



ASPIRE STUDIED  
792 PATIENTS WITH  
RELAPSED MULTIPLE  
MYELOMA<sup>3</sup>

RESULTS PUBLISHED  
IN THE NEW  
ENGLAND JOURNAL  
OF MEDICINE<sup>3</sup>

## **MEDIA INQUIRIES**

Kristen Davis, +1 (805) 447-3008, [kristend@amgen.com](mailto:kristend@amgen.com) Trish Hawkins, +1 (805) 447-5631, [plange@amgen.com](mailto:plange@amgen.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)

## **FORWARD-LOOKING STATEMENTS**

This fact sheet 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 July 24, 2015 and expressly disclaims any duty to update information contained in this fact sheet.

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 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.

## **IMPORTANT SAFETY INFORMATION REGARDING KYPROLIS® (CARFILZOMIB) FOR INJECTION**

### **WARNINGS AND PRECAUTIONS**

#### **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. In clinical studies with Kyprolis, these events typically occurred early in the course of Kyprolis therapy (< 5 cycles). Death due to cardiac arrest has occurred within a day of Kyprolis administration. 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, all patients should also be monitored 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. In patients ≥ 75 years of age, the risk of cardiac failure is increased. Patients with New York Heart Association Class III and IV heart failure, recent myocardial infarction, and conduction abnormalities uncontrolled by medications were not eligible for the clinical trials. These patients may be at greater risk for cardiac complications.

#### **Acute Renal Failure:**

Cases of acute renal failure have occurred in patients receiving Kyprolis. Renal insufficiency adverse events (renal impairment, acute renal failure, renal failure) have occurred with an incidence of approximately 8% in a randomized controlled trial. Acute renal failure was reported more frequently in patients with advanced relapsed and refractory multiple myeloma who received Kyprolis monotherapy. This risk was greater in patients with a baseline reduced estimated creatinine clearance (calculated using Cockcroft and Gault equation). 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 been reported in patients who received Kyprolis. Patients with multiple myeloma and a high tumor burden should be considered to be at greater risk for TLS. Ensure that patients are well hydrated before administration of Kyprolis 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 including interruption of 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 less than 1% of 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 approximately 1% of patients treated with Kyprolis and was Grade 3 or greater in less than 1% of patients. Evaluate with cardiac imaging and/or other tests as indicated. Withhold Kyprolis for pulmonary hypertension until resolved or returned to baseline and consider whether to restart Kyprolis based on a benefit/risk assessment.

#### **Dyspnea:**

Dyspnea was reported in 28% of patients treated with Kyprolis and was Grade 3 or greater in 4% of patients. 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. In the combination study, the incidence of venous thromboembolic events in the first 12 cycles was 13% in the Kyprolis combination arm versus 6% in the control arm. With Kyprolis monotherapy, the incidence of venous thromboembolic events was 2%. Thromboprophylaxis is recommended and should be based on an assessment of the patient's underlying risks, treatment regimen, and clinical status.

#### **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. Administer dexamethasone prior to Kyprolis to reduce the incidence and severity of infusion reactions. Inform patients of the risk and of symptoms and to contact a physician immediately if symptoms of an infusion reaction occur.

**Thrombocytopenia:**

Kyprolis causes thrombocytopenia with platelet nadirs observed between Day 8 and Day 15 of each 28-day cycle with recovery to baseline platelet count usually by the start of the next cycle. Thrombocytopenia was reported in approximately 40% of patients in clinical trials with 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 (< 1%) during treatment with Kyprolis. Kyprolis can cause increased serum transaminases. Monitor liver enzymes regularly. Reduce or withhold dose as appropriate.

**Thrombotic Thrombocytopenic Purpura /Hemolytic Uremic Syndrome:**

Cases of thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS) including fatal outcome have been reported in patients who received Kyprolis. Monitor for signs and symptoms of TTP/HUS. If the diagnosis is suspected, stop Kyprolis and evaluate. 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 been reported in patients receiving Kyprolis. Posterior reversible encephalopathy syndrome (PRES), formerly termed Reversible Posterior Leukoencephalopathy Syndrome (RPLS), is a neurological disorder which can present with seizure, headache, lethargy, confusion, blindness, altered consciousness, and other visual and neurological disturbances, along with hypertension, and the diagnosis is confirmed by neuro-radiological imaging (MRI). 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. There are no adequate and well-controlled studies in pregnant women using Kyprolis. Kyprolis caused embryo-fetal toxicity in pregnant rabbits at doses that were lower than in patients receiving the recommended dose. Females of reproductive potential should be advised to avoid becoming pregnant while being treated with Kyprolis. If this drug is used during pregnancy, or if the patient becomes pregnant 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 trial: decreased lymphocytes, decreased absolute neutrophil count, decreased phosphorus, anemia, neutropenia, decreased total white blood cell count, decreased platelets, diarrhea, fatigue, thrombocytopenia, pyrexia, muscle spasm, cough, upper respiratory tract infection, decreased hemoglobin, hypokalemia.

**USE IN SPECIFIC POPULATIONS**

Patients on dialysis: Administer Kyprolis after the dialysis procedure.

**POST-MARKETING EXPERIENCE**

The following adverse reactions were reported in the post-marketing experience: dehydration, thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), tumor lysis syndrome including fatal outcomes, and posterior reversible encephalopathy syndrome (PRES). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Full prescribing information is available at [www.kyprolis.com](http://www.kyprolis.com)

**REFERENCES**

1. KYPROLIS [prescribing information]. South San Francisco, CA: Onyx Pharmaceuticals, Inc.; 2015.
2. International Myeloma Foundation. Understanding Protein Electrophoresis. [http://myeloma.org/pdfs/U-PEP-Eng2012%28P%29\\_f1web.pdf](http://myeloma.org/pdfs/U-PEP-Eng2012%28P%29_f1web.pdf) Accessed July 2015.
3. KYPROLIS [patient information leaflet]. South San Francisco, CA: Onyx Pharmaceuticals, Inc.; 2014.
4. Stewart KA, Rajkumar VS, Dimopoulos MA, et al. Carfilzomib, Lenalidomide, and Dexamethasone for Relapsed Multiple Myeloma. *N Engl J Med*. 2015; 372:142-152.