HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use KYPROLIS safely and effectively. See full prescribing information for KYPROLIS.

KYPROLIS® (carfilzomib) for injection, for intravenous use
Initial U.S. Approval: 2012

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	7/2015
Dosage and Administration (2.1)	7/2015
Warnings and Precautions (5)	7/2015

----------INDICATIONS AND USAGE----------

Kyprolis is a proteasome inhibitor that is indicated

- in combination with lenalidomide and dexamethasone for the treatment of patients with relapsed multiple myeloma who have received one to three prior lines of therapy . (1, 14)
- as a single agent for the treatment of patients with multiple myeloma who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval is based on response rate. Clinical benefit, such as improvement in survival or symptoms, has not been verified. (1, 14)

----------DOSAGE AND ADMINISTRATION----------

- Hydrate prior to and following administration.as needed. (2.1)
- Premedicate with dexamethasone prior to all Cycle 1 doses and if infusion reaction symptoms develop or reappear. (2.1, 2.2)
- Administer intravenously as a 10 minute infusion on two consecutive days each week for three weeks (Days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest period (Days 17 to 28). (2.1, 2.2)
- Kyprolis is administered at a starting dose of 20 mg/m^2/day in Cycle 1 on Days 1 and 2. If tolerated, the dose should be escalated to a target dose of 27 mg/m^2/day on Day 8 of Cycle 1. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

For injection: 60 mg, lyophilized powder in single-dose vial for reconstitution (3)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

- Cardiac toxicities include cardiac failure and myocardial infarction with fatal outcome, and myocardial ischemia. Withhold Kyprolis and evaluate promptly. (5.1)
- Acute Renal Failure: Monitor serum creatinine regularly (5.2)
- Tumor Lysis Syndrome (TLS): Administer pre-treatment hydration. (2.1) Monitor for TLS, including uric acid levels and treat promptly. (5.3)
- Pulmonary Toxicity: including Acute Respiratory Distress Syndrome, acute respiratory failure, and acute diffuse infiltrative pulmonary disease: Withhold Kyprolis and evaluate promptly (5.4)
- Pulmonary Hypertension: Withhold Kyprolis and evaluate(5.5)
- Dyspnea: For severe or life threatening dyspnea, withhold Kyprolis and evaluate. (5.6)
- Hypertension including hypertensive crisis: Monitor blood pressure regularly. If hypertension cannot be adequately controlled, a risk-benefit decision on continued Kyprolis therapy is needed. (5.7)
- Venous Thrombosis: Thromboprophylaxis is recommended. (5.8)
- Infusion Reactions: Pre-medicate with dexamethasone. (2.1, 5.9)
- Thrombocytopenia: Monitor platelet counts; interrupt or reduce Kyprolis dosing as clinically indicated. (2.4, 5.10)
- Hepatic Toxicity and Hepatic Failure: Monitor liver enzymes. Withhold Kyprolis if suspected. (5.11)
- Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS). Monitor for signs and symptoms of TTP/HUS. Discontinue Kyprolis if suspected. (5.12)
- Posterior reversible encephalopathy syndrome (PRES): Consider neuro-radiological imaging (MRI) for onset of visual or neurological symptoms; discontinue Kyprolis if suspected. (5.13)
- Embryo-fetal Toxicity: Kyprolis can cause fetal harm. Females of reproductive potential should avoid becoming pregnant while being treated. (5.14, 8.1)

----------ADVERSE REACTIONS----------

The most common adverse events occurring in at least 20% of patients treated with Kyprolis in monotherapy trials: anemia, fatigue, thrombocytopenia, nausea, pyrexia, decreased platelets, dyspnea, diarrhea, decreased lymphocyte, headache, decreased hemoglobin, cough, edema peripheral.

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.

To report SUSPECTED ADVERSE REACTIONS, contact Onyx Pharmaceuticals, Inc. at 1-877-669-9121 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------USE IN SPECIFIC POPULATIONS----------

- In the Kyprolis clinical trials, the incidence of adverse events was greater in patients ≥ 75 years of age. (8.5)
- Patients on dialysis: Administer Kyprolis after the dialysis procedure. (8.6)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 7/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Combination Therapy

Kyprolis in combination with lenalidomide and dexamethasone is indicated for the treatment of patients with relapsed multiple myeloma who have received one to three prior lines of therapy. [*see Clinical Studies (14.1)*].

1.2 Monotherapy

Kyprolis is indicated as a single agent for the treatment of patients with multiple myeloma who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy [*see Clinical Studies (14.2)*]. Approval is based on response rate. Clinical benefit, such as improvement in survival or symptoms, has not been verified. (1, 14)

2 DOSAGE AND ADMINISTRATION

2.1 Administration Precautions

- **Hydration** - Adequate hydration is required prior to dosing in Cycle 1, especially in patients at high risk of tumor lysis syndrome or renal toxicity. The recommended hydration includes both oral fluids (30 mL per kg at least 48 hours before Cycle 1, Day 1) and intravenous fluids (250 mL to 500 mL of appropriate intravenous fluid prior to each dose in Cycle 1). If needed, give an additional 250 mL to 500 mL of intravenous fluids following Kyprolis administration. Continue oral and/or intravenous hydration, as needed, in subsequent cycles. Monitor patients for evidence of volume overload and adjust hydration to individual patient needs, especially in patients with or at risk for cardiac failure [*see Warnings and Precautions (5)*].
- **Premedications** - Premedicate with dexamethasone 4 mg for monotherapy (or the recommended dexamethasone dose if on combination therapy [*see Dosage and Administration (2.2)*]) orally or intravenously at least 30 minutes but no more than 4 hours prior to all doses of Kyprolis during Cycle 1 to reduce the incidence and severity of

infusion reactions [*see Warnings and Precautions (5.5)*]. Reinstate dexamethasone premedication if these symptoms occur during subsequent cycles.

- **Administration** - Infuse over 10 minutes. Do not administer as a bolus. Flush the intravenous administration line with normal saline or 5% dextrose injection, USP immediately before and after Kyprolis administration. Do not mix Kyprolis with or administer as an infusion with other medicinal products.
- **Dose Calculation** - Calculate the Kyprolis dose [*see Dosage and Administration (2.2)*] using the patient's actual body surface area at baseline. Patients with a body surface area greater than 2.2 m^2 should receive a dose based upon a body surface area of 2.2 m^2.
- **Thromboprophylaxis** - Thromboprophylaxis is recommended for patients being treated with the combination of Kyprolis, lenalidomide and dexamethasone. The thromboprophylaxis regimen should be based on an assessment of the patient's underlying risks. [*see Warnings and Precautions (5.8)*]
- **Infection Prophylaxis** - Consider antiviral prophylaxis in patients being treated with Kyprolis to decrease the risk of herpes zoster reactivation.

2.2 Recommended Dosing

Kyprolis in Combination with Lenalidomide and Dexamethasone

For the combination regimen, administer Kyprolis intravenously as a 10 minute infusion on two consecutive days, each week for three weeks followed by a 12 day rest period as shown in Table 1. Each 28-day period is considered one treatment cycle. The recommended starting dose of Kyprolis is 20 mg/m^2 in Cycle 1 on Days 1 and 2. If tolerated, escalate to a target dose of 27 mg/m^2 on Day 8 of Cycle 1. From Cycle 13, omit the Day 8 and 9 doses of Kyprolis. Discontinue Kyprolis after Cycle 18. Lenalidomide 25 mg is taken orally on Days 1–21 and dexamethasone 40 mg by mouth or intravenously on Days 1, 8, 15, and 22 of the 28-day cycles.

Table 1: Kyprolis in Combination with Lenalidomide and Dexamethasone

	Cycle 1										
	Week 1			Week 2			Week 3			Week 4	
	Day 1	Day 2	Days 3–7	Day 8	Day 9	Days 10–14	Day 15	Day 16	Days 17–21	Day 22	Days 23-28
Kyprolis (mg/m^2):	20	20	-	27	27	-	27	27	-	-	-
Dexamethasone	40 mg	-	-	40 mg	-	-	40 mg	-	-	40 mg	-
Lenalidomide	25 mg daily									-	-
	Cycles 2 to 12										
	Week 1			**Week 2**			**Week 3**			**Week 4**	
	Day 1	**Day 2**	**Days 3–7**	**Day 8**	**Day 9**	**Days 10–14**	**Day 15**	**Day 16**	**Days 17–21**	**Day 22**	**Days 23-28**
Kyprolis (mg/m^2):	27	27	-	27	27	-	27	27	-	-	-
Dexamethasone	40 mg	-	-	40 mg	-	-	40 mg	-	-	40 mg	-
Lenalidomide	25 mg daily									-	-
	Cycles 13 on[a]										
	Week 1			**Week 2**			**Week 3**			**Week 4**	
	Day 1	**Day 2**	**Days 3–7**	**Day 8**	**Day 9**	**Days 10–14**	**Day 15**	**Day 16**	**Days 17–21**	**Day 22**	**Days 23-28**
Kyprolis (mg/m^2):	27	27	-	-	-	-	27	27	-	-	-
Dexamethasone	40 mg	-	-	40 mg	-	-	40 mg	-	-	40 mg	-
Lenalidomide	25 mg daily										

[a] Kyprolis is administered through Cycle 18, lenalidomide and dexamethasone continue thereafter.

Continue treatment until disease progression or unacceptable toxicity occurs. Refer to the lenalidomide and dexamethasone Prescribing Information for other concomitant medications, such as the use of anticoagulant and antacid prophylaxis, that may be required with those agents.

Kyprolis Monotherapy

For monotherapy, administer Kyprolis intravenously as a 10 minute infusion on two consecutive days, each week for three weeks followed by a 12 day rest period as shown in Table 2. Each 28-day period is considered one treatment cycle. The recommended starting dose of Kyprolis is 20 mg/m^2 in Cycle 1 on Days 1 and 2. If tolerated, escalate to a target dose of 27 mg/m^2 on Day 8 of Cycle 1. From Cycle 13, omit the Day 8 and 9 doses of Kyprolis. Continue treatment until disease progression or unacceptable toxicity occurs.

Table 2: Kyprolis Monotherapy

	Cycle 1									
	Week 1			**Week 2**			**Week 3**			**Week 4**
	Day 1	**Day 2**	**Days 3–7**	**Day 8**	**Day 9**	**Days 10–14**	**Day 15**	**Day 16**	**Days 17–21**	**Days 22–28**
Kyprolis (mg/m^2):	20	20	-	27	27	-	27	27	-	-
	Cycles 2 to 12									
	Week 1			**Week 2**			**Week 3**			**Week 4**
	Day 1	**Day 2**	**Days 3–7**	**Day 8**	**Day 9**	**Days 10–14**	**Day 15**	**Day 16**	**Days 17–21**	**Days 22–28**
Kyprolis (mg/m^2):	27	27	-	27	27	-	27	27	-	-
	Cycles 13 on									
	Week 1			**Week 2**			**Week 3**			**Week 4**
	Day 1	**Day 2**	**Days 3–7**	**Day 8**	**Day 9**	**Days 10–14**	**Day 15**	**Day 16**	**Days 17–21**	**Days 22–28**
Kyprolis (mg/m^2):	27	27	-	-	-	-	27	27	-	-

2.3 Dose Modifications Based on Toxicities

Modify dosing based on toxicity. Recommended actions and dose modifications for Kyprolis are presented in Table 3. See the lenalidomide and dexamethasone Prescribing Information respectively for dosingrecommendations.

Table 3: Dose Modifications for Toxicity[a] during Kyprolis Treatment

Hematologic Toxicity	Recommended Action
• Absolute neutrophil count < 0.5 x10^9/L	• Withhold dose • If recovered to ≥ 0.5 x10^9/L, continue at the same dose level • For subsequent drops to < 0.5 x10^9/L, follow the same recommendations as above and consider 1 dose level reduction when restarting Kyprolis[a]
• Platelets <10 x10^9/L or evidence of bleeding with thrombocytopenia [*see Warnings and Precautions (5)*]	• Withhold dose • If recovered to ≥ 10 x10^9/L and/or bleeding is controlled, continue at the same dose level • For subsequent drops to < 10 x10^9 /L, follow the same recommendations as above and consider 1 dose level reduction when restarting Kyprolis[a]
Renal Toxicity	**Recommended Action**

• Serum creatinine ≥ 2 × baseline, or
• Creatinine clearance < 15 mL/min, or creatinine clearance decreases to ≤ 50% of baseline, or need for dialysis
[*see Warnings and Precautions (5)*]
	• Withhold dose and continue monitoring renal function (serum creatinine or creatinine clearance)
	  • If attributable to Kyprolis, resume when renal function has recovered to within 25% of baseline; start at 1 dose level reduction[a]
	  • If not attributable to Kyprolis, dosing may be resumed at the discretion of the physician
	• For patients on dialysis receiving Kyprolis, the dose is to be administered after the dialysis procedure

Other Non-hematologic Toxicity	**Recommended Action**
• All other severe or life-threatening[b] non-hematological toxicities	• Withhold until resolved or returned to baseline • Consider restarting the next scheduled treatment at 1 dose level reduction[a]

[a] From 27 mg/m^2 to 20 mg/m^2 or from 20 mg/m^2 to 15 mg/m^2 is considered 1 dose level reduction.

[b] CTCAE Grades 3 and 4

2.4 Reconstitution and Preparation for Intravenous Administration

Kyprolis vials contain no antimicrobial preservatives and are intended for single use only. Unopened vials of Kyprolis are stable until the date indicated on the package when stored in the original package at 2°C to 8°C (36°F to 46°F). The reconstituted solution contains carfilzomib at a concentration of 2 mg/mL. The quantity of Kyprolis contained in one single-dose vial (60 mg carfilzomib) may exceed the required dose. Caution should be used in calculating the quantity delivered to prevent overdosing. Read the complete preparation instructions prior to reconstitution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Reconstitution/Preparation Steps:

1. Remove vial from refrigerator just prior to use.
2. Calculate the dose (mg/m^2) and number of vials of Kyprolis required using the patient's body surface area (BSA) at baseline. Patients with a BSA greater than 2.2 m^2 should receive a dose based upon a BSA of 2.2 m^2. Dose adjustments do not need to be made for weight changes of less than or equal to 20%.
   a. Aseptically reconstitute each vial by slowly injecting **29 mL** Sterile Water for Injection, USP, through the stopper and directing the solution onto the INSIDE WALL OF THE VIAL to minimize foaming.

3. Gently swirl and/or invert the vial slowly for about 1 minute, or until complete dissolution. DO NOT SHAKE to avoid foam generation. If foaming occurs, allow the solution to settle in the vial until foaming subsides (approximately 5 minutes) and the solution is clear.
4. Visually inspect for particulate matter and discoloration prior to administration.. The reconstituted product should be a clear, colorless solution and should not be administered if any discoloration or particulate matter is observed.
5. Discard any unused portion left in the vial.
6. Optionally, Kyprolis can be administered in an IV bag.
7. When administering in an intravenous bag, withdraw the calculated dose [*see Dosage and Administration (2)*] from the vial and dilute into **50 mL** IV bag containing 5% Dextrose Injection, USP.

The stabilities of reconstituted Kyprolis under various temperature and container conditions are shown in Table 4.

Table 4: Stability of Reconstituted Kyprolis

Storage Conditions of Reconstituted Kyprolis	Stability[a] per Container		
	Vial	Syringe	IV Bag (D5W[b])
Refrigerated (2°C to 8°C; 36°F to 46°F)	24 hours	24 hours	24 hours
Room Temperature (15°C to 30°C; 59°F to 86°F)	4 hours	4 hours	4 hours

[a] Total time from reconstitution to administration should not exceed 24 hours
[b] 5% Dextrose Injection, USP

3 DOSAGE FORMS AND STRENGTHS

Kyprolis single-dose vial contains 60 mg of carfilzomib as a sterile, white to off-white lyophilized cake or powder.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 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 [*see Dosage and Administration (2)*].

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 [*see Dosage and Administration (2)*].

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 [*see Use in Specific Populations (8)*].

5.2 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 [*see Dosage and Administration (2)*].

5.3 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 [*see Dosage and Administration (2)*]. 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 [*see Dosage and Administration (2)*].

5.4 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. [*see Dosage and Administration (2)*].

5.5 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 [*see Dosage and Administration (2)*].

5.6 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 [*see Dosage and Administration (2.3), Cardiac Disorders (5.1), Pulmonary Toxicity (5.2), and Adverse Reactions (6)*].

5.7 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 [*see Dosage and Administration (2)*].

5.8 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.

5.9 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 [*see Dosage and Administration (2)*]. Inform patients of the risk and of symptoms and to contact a physician immediately if symptoms of an infusion reaction occur [*see Patient Counseling Information (17)*].

5.10 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 [*see Adverse Reactions (6)*]. 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 [*see Dosage and Administration (2)*].

5.11 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 [*see Dosage and Administration (2) and Adverse Reactions (6)*].

5.12 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.

5.13 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.

5.14 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. Carfilzomib 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 [*see Use in Specific Populations (8.1)*].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Cardiac Toxicities [*see Warnings and Precautions (5.1)*]
- Acute Kidney Injury [*see Warnings and Precautions (5.2)*]
- Tumor Lysis Syndrome [*see Warnings and Precautions (5.3)*]
- Pulmonary Toxicity [*see Warnings and Precautions (5.4)*]
- Pulmonary Hypertension[*see Warnings and Precautions (5.5)*]
- Dyspnea [*see Warnings and Precautions (5.6)*]
- Hypertension [*see Warnings and Precautions (5.7)]*
- Venous Thromboses [*see Warnings and Precautions (5.8)*]
- Infusion Reactions [*see Warnings and Precautions (5.9)*]
- Thrombocytopenia [*see Warnings and Precautions (5.10)*]
- Hepatic Toxicity and Hepatic Failure [*see Warnings and Precautions (5.11)*]
- Thrombotic Thrombocytopenic Purpura /Hemolytic Uremic Syndrome [*see Warnings and Precautions (5.12)*]
- Posterior Reversible Encephalopathy Syndrome (PRES) [*see Warnings and Precautions (5.13)]*

6.1 Clinical Trials Safety Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug, and may not reflect the rates observed in medical practice.

6.1.1 Safety Experience with Kyprolis in Combination with Lenalidomide and Dexamethasone in Patients with Multiple Myeloma

The safety of Kyprolis in combination with lenalidomide and dexamethasone (KRd) was evaluated in an open-label randomized study in patients with relapsed multiple myeloma. Details of the study treatment are described in Section 14.1. The median number of cycles initiated was 22 cycles for the KRd arm and 14 cycles for the Rd arm.

Deaths due to adverse events within 30 days of the last dose of any therapy in the KRd arm occurred in 27/392 (7%) patients compared with 27/389 (7%) patients who died due to adverse events within 30 days of the last dose of any Rd therapy. The most common cause of deaths occurring in patients (%) in the two arms (KRd vs. Rd) included cardiac 10 (3%) vs. 7 (2%), infection 9 (2%) vs. 10 (3%), renal 0 (0%) vs. 1 (< 1%), and other adverse events 9 (2%) vs. 10 (3%). Serious adverse events were reported in 60% of the patients in the KRd arm and 54% of the patients in the Rd arm. The most common serious adverse events reported in the KRd arm as compared with the Rd arm were pneumonia (14% vs. 11%), respiratory tract infection (4% vs. 1.5%), pyrexia (4% vs. 2%), and pulmonary embolism (3% vs. 2%). Discontinuation due to any adverse event occurred in 26% in the KRd arm vs. 25% in the Rd arm. Adverse events leading to discontinuation of Kyprolis occurred in 12% of patients and the most common events included pneumonia (1%), myocardial infarction (0.8%), and upper respiratory tract infection (0.8%).

Common Adverse Events (≥ 10%)

The adverse events in the first 12 cycles of therapy that occurred at a rate of 10% or greater in the KRd arm are presented in Table 5.

Table 5: Common Adverse Events (≥ 10% in the KRd Arm) Occurring in Cycles 1–12 (Combination Therapy)

System Organ Class	KRd Arm (N = 392)		Rd Arm (N = 389)	
Preferred Term	**Any Grade**	**≥ Grade 3**	**Any Grade**	**≥ Grade 3**
Blood and Lymphatic System Disorders				
Anemia	138 (35%)	53 (14%)	127 (33%)	47 (12%)
Neutropenia	124 (32%)	104 (27%)	115 (30%)	89 (23%)
Thrombocytopenia	100 (26%)	58 (15%)	75 (19%)	39 (10%)
Gastrointestinal Disorders				
Diarrhea	115 (29%)	7 (2%)	105 (27%)	12 (3%)
Constipation	68 (17%)	0	53 (14%)	1 (0%)
Nausea	60 (15%)	1 (0%)	39 (10%)	3 (1%)
General Disorders and Administration Site Conditions				
Fatigue	109 (28%)	21 (5%)	104 (27%)	20 (5%)
Pyrexia	93 (24%)	5 (1%)	64 (17%)	1 (0%)
Edema Peripheral	63 (16%)	2 (1%)	57 (15%)	2 (1%)
Asthenia	53 (14%)	11 (3%)	46 (12%)	7 (2%)
Infections and Infestations				
Upper Respiratory Tract Infection	85 (22%)	7 (2%)	52 (13%)	3 (1%)
Nasopharyngitis	63 (16%)	0	43 (11%)	0
Bronchitis	54 (14%)	5 (1%)	39 (10%)	2 (1%)
Pneumonia[a]	54 (14%)	35 (9%)	43 (11%)	27 (7%)
Metabolism and Nutrition Disorders				
Hypokalemia	78 (20%)	22 (6%)	35 (9%)	12 (3%)
Hypocalcemia	55 (14%)	10 (3%)	39 (10%)	5 (1%)
Hyperglycemia	43 (11%)	18 (5%)	33 (9%)	15 (4%)
Musculoskeletal and Connective Tissue Disorders				
Muscle Spasms	88 (22%)	3 (1%)	73 (19%)	3 (1%)
Nervous System Disorders				
Peripheral Neuropathies NEC[b]	43 (11%)	7 (2%)	37 (10%)	4 (1%)
Psychiatric Disorders				
Insomnia	63 (16%)	6 (2%)	50 (13%)	8 (2%)
Respiratory, Thoracic, and Mediastinal Disorders				
Cough	85 (22%)	1 (0%)	46 (12%)	0
Dyspnea[c]	70 (18%)	9 (2%)	58 (15%)	6 (2%)
Skin and Subcutaneous Tissue Disorders				

Rash	45 (12%)	5 (1%)	53 (14%)	5 (1%)
Vascular Disorders				
Embolic and Thrombotic Events, Venous[d]	49 (13%)	16 (4%)	22 (6%)	9 (2%)
Hypertension[e]	41 (11%)	12 (3%)	15 (4%)	4 (1%)

KRd = Kyprolis, lenalidomide, and low-dose dexamethasone; Rd = lenalidomide and low-dose dexamethasone

[a] Pneumonia includes preferred terms of pneumonia, bronchopneumonia

[b] Peripheral neuropathies NEC includes preferred terms under HLT peripheral neuropathies NEC

[c] Dyspnea includes preferred terms of dyspnea, dyspnea exertional

[d] Embolic and thrombotic events, venous include preferred terms in MedDRA SMQ narrow scope search of embolic and thrombotic events, venous.

[e] Hypertension includes preferred terms of hypertension, hypertensive crisis, hypertensive emergency

There were 274 (70%) patients in the KRd arm who received treatment beyond Cycle 12.

There were no new clinically relevant AEs that emerged in the later treatment cycles.

Adverse Reactions Occurring at a Frequency of < 10%

- **Blood and lymphatic system disorders**: febrile neutropenia, lymphopenia,
- **Cardiac disorders**: cardiac arrest, cardiac failure, cardiac failure congestive, myocardial infarction, myocardial ischemia
- **Eye disorders:** cataract, vision blurred
- **Gastrointestinal disorders:** abdominal pain, abdominal pain upper, dyspepsia, toothache
- **General disorders and administration site conditions:** chills**,** infusion site reaction, multi-organ failure, pain
- **Infections and infestations:** influenza, sepsis, urinary tract infection, viral infection
- **Metabolism and nutrition disorders:** dehydration, hyperkalemia, hyperuricemia, hypoalbuminemia, hyponatremia, tumor lysis syndrome
- **Musculoskeletal and connective tissue disorders**: muscular weakness, myalgia
- **Nervous system disorders**: hypoesthesia, paresthesia, deafness
- **Psychiatric disorders**: anxiety, delirium
- **Renal and urinary disorders**: renal failure, renal failure acute, renal impairment
- **Respiratory, thoracic and mediastinal disorders**: dysphonia, epistaxis, oropharyngeal pain, pulmonary embolism, pulmonary edema
- **Skin and subcutaneous tissue disorders**: erythema, hyperhidrosis, pruritus
- **Vascular disorders**: deep vein thrombosis, hypotension

Grade 3 and higher adverse reactions that occurred during Cycles 1-12 with a substantial difference (≥ 2%) between the two arms were neutropenia, thrombocytopenia, hypokalemia, and hypophosphatemia.

Laboratory Abnormalities

Table 6 describes Grade 3–4 laboratory abnormalities reported at a rate of ≥10% in the KRd arm for patients who received combination therapy.

Table 6: Grade 3–4 Laboratory Abnormalities (≥ 10%) in Cycles 1-12 (Combination Therapy)

Laboratory Abnormality	KRd (N = 392)	Rd (N = 389)
Decreased Lymphocytes	182 (46%)	119 (31%)
Decreased Absolute Neutrophil Count	152 (39%)	140 (36%)
Decreased Phosphorus	122 (31%)	106 (27%)
Decreased Platelets	101 (26%)	59 (15%)
Decreased Total White Blood Cell Count	97 (25%)	71 (18%)
Decreased Hemoglobin	58 (15%)	68 (18%)
Decreased Potassium	41 (11%)	23 (6%)

KRd = Kyprolis, lenalidomide, and low-dose dexamethasone; Rd = lenalidomide and low-dose dexamethasone

6.1.2 Safety Experience with Kyprolis in Patients with Multiple Myeloma who Received Monotherapy

The safety of Kyprolis was evaluated in clinical trials in which 598 patients with relapsed and/or refractory myeloma received Kyprolis monotherapy starting with the 20 mg/m^2 dose in Cycle 1 Day 1 and escalating to 27 mg/m^2 on Cycle 1 Day 8 or Cycle 2 Day 1. The median age of these patients was 64 years (range 32–87) . The patients received a median of 5 (range 1–20) prior regimens. Approximately 57% of the patients were male. The median number of cycles initiated was 4 (range 1–35).

Serious adverse events were reported, regardless of causality, in 50% of patients in the pooled Kyprolis monotherapy studies (n = 598). The most common serious adverse events were: pneumonia (8%), acute renal failure (5%), disease progression (4%), pyrexia (3%),

hypercalcemia (3%), congestive heart failure (3%), multiple myeloma (3%), anemia (2%), and dyspnea (2%). In patients treated with Kyprolis, the incidence of serious adverse events was higher in those ≥65 years old and in those ≥75 years old [see Geriatric Use (8.5)].

Deaths due to adverse events within 30 days of the last dose of Kyprolis occurred in 30/598 (5%) patients receiving Kyprolis monotherapy. These adverse events were related to cardiac disorders in 10 (2%) patients, infections in 8 (1%) patients, renal disorders in 4 (< 1%) patients, and other adverse events in 8 (1%) patients. In a randomized trial comparing Kyprolis as a single agent versus corticosteroids with optional oral cyclophosphamide for patients with relapsed and refractory multiple myeloma, mortality was higher in the patients treated with Kyprolis in comparison to the control arm in the subgroup of 48 patients ≥75 years of age.

The most common cause of discontinuation due to an adverse event was acute renal failure (2%). The common adverse events occurring at a rate of 10% or greater with Kyprolis monotherapy are presented in Table 7.

Table 7: Most Commonly Reported Adverse Events (≥ 10%) with Kyprolis Monotherapy

System Organ Class	Kyprolis Monotherapy 20/27 mg/m^2 (N = 598)	
	Any Grade	≥ Grade 3
Blood and Lymphatic System Disorders		
Anemia	291 (49%)	141 (24%)
Thrombocytopenia	220 (37%)	152 (25%)
Neutropenia	113 (19%)	63 (11%)
Lymphopenia	85 (14%)	73 (12%)
Leukopenia	61 (10%)	26 (4%)
Gastrointestinal Disorders		
Nausea	211 (35%)	7 (1%)
Diarrhea	160 (27%)	8 (1%)
Vomiting	104 (17%)	4 (1%)
Constipation	90 (15%)	1 (0%)
General Disorders and Administration Site Conditions		
Fatigue	238 (40%)	25 (4%)
Pyrexia	177 (30%)	11 (2%)

Edema Peripheral	118 (20%)	1 (0%)
Chills	73 (12%)	1 (0%)
Asthenia	71 (12%)	9 (2%)
Infections and Infestations		
Upper Respiratory Tract Infection	112 (19%)	15 (3%)
Pneumonia[a]	71 (12%)	54 (9%)
Metabolism and Nutrition Disorders		
Decreased Appetite	89 (15%)	2 (0%)
Hypercalcemia	68 (11%)	26 (4%)
Hypokalemia	61 (10%)	17 (3%)
Musculoskeletal and Connective Tissue Disorders		
Back Pain	115 (19%)	19 (3%)
Arthralgia	83 (14%)	5 (1%)
Pain in Extremity	69 (12%)	7 (1%)
Muscle Spasms	62 (10%)	2 (0%)
Musculoskeletal Pain	60 (10%)	12 (2%)
Nervous System Disorders		
Headache	141 (24%)	7 (1%)
Dizziness	64 (11%)	5 (1%)
Peripheral Neuropathies NEC[b]	62 (10%)	5 (1%)
Psychiatric Disorders		
Insomnia	75 (13%)	0
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnea[c]	202 (34%)	21 (4%)
Cough	120 (20%)	2 (0%)
Epistaxis	60 (10%)	5 (1%)
Renal Disorders		
Renal Failure	76 (13%)	49 (8%)
Vascular Disorders		
Hypertension[d]	90 (15%)	22 (4%)

[a] Pneumonia includes the preferred terms of pneumonia, bronchopneumonia.
[b] Peripheral neuropathies NEC includes the preferred terms under HLT peripheral neuropathies NEC.
[c] Dyspnea includes the preferred terms of dyspnea, dyspnea exertional.
[d] Hypertension includes the preferred terms of hypertension, hypertensive crisis, and hypertensive emergency.

Adverse Reactions Occurring at a Frequency of < 10%

- **Blood and lymphatic system disorders**: febrile neutropenia

- **Cardiac disorders**: cardiac arrest, cardiac failure congestive, myocardial infarction, myocardial ischemia
- **Eye disorders:** cataract, blurred vision
- **Gastrointestinal disorders:** abdominal pain, abdominal pain upper, dyspepsia, toothache
- **General disorders and administration site conditions**: infusion site reaction, multi-organ failure, pain
- **Hepatobiliary disorders**: hepatic failure
- **Infections and infestations:** bronchitis, influenza, nasopharyngitis, respiratory tract infection, sepsis, urinary tract infection
- **Metabolism and nutrition disorders:** hyperglycemia, hyperkalemia, hyperuricemia, hypoalbuminemia, hypocalcemia, hypomagnesemia, hyponatremia, hypophosphatemia, tumor lysis syndrome
- **Musculoskeletal and connective tissue disorders**: musculoskeletal chest pain, myalgia
- **Nervous system disorders**: hypoesthesia, paresthesia
- **Psychiatric disorders**: anxiety
- **Renal and urinary disorders**: renal impairment
- **Respiratory, thoracic and mediastinal disorders**: dysphonia, oropharyngeal pain, pulmonary edema
- **Skin and subcutaneous tissue disorders**: erythema, hyperhidrosis, pruritus, rash
- **Vascular disorders**: embolic and thrombotic events, venous (including deep vein thrombosis and pulmonary embolism), hypotension

Grade 3 and higher adverse reactions occurring at an incidence of >1% include febrile neutropenia, cardiac arrest, cardiac failure congestive, pain, sepsis, urinary tract infection, hyperglycemia, hyperkalemia, hyperuricemia, hypoalbuminemia, hypocalcemia**,** hyponatremia, hypophosphatemia, renal failure, renal failure acute, renal impairment, pulmonary edema, and hypotension.

Laboratory Abnormalities

Table 8 describes Grade 3–4 laboratory abnormalities reported at a rate of > 10% for patients who received Kyprolis monotherapy.

Table 8: Grade 3–4 Laboratory Abnormalities (> 10%) (Monotherapy)

Adverse Reaction	Kyprolis (N = 598)
Decreased Platelets	184 (31%)
Decreased Lymphocytes	151 (25%)
Decreased Hemoglobin	132 (22%)
Decreased Total White Blood Cell Count	71 (12%)
Decreased Sodium	69 (12%)
Decreased Absolute Neutrophil Count	67 (11%)

6.2 Post-marketing Experience

The following adverse reactions were reported in the post-marketing experience with Kyprolis. 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: dehydration, thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), tumor lysis syndrome including fatal outcomes, and posterior reversible encephalopathy syndrome (PRES).

7 DRUG INTERACTIONS

Carfilzomib is primarily metabolized via peptidase and epoxide hydrolase activities, and as a result, the pharmacokinetic profile of carfilzomib is unlikely to be affected by concomitant administration of cytochrome P450 inhibitors and inducers. Carfilzomib is not expected to influence exposure of other drugs [*see Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Kyprolis, a proteasome inhibitor, may cause fetal harm based on findings from animal studies [*see Data*] and the drug's mechanism of action [*see Clinical Pharmacology (12.1)*]. 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. Consider the benefits and risks of Kyprolis and possible risks to the fetus when prescribing Kyprolis to a pregnant woman. If Kyprolis is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%–4% and 15%–20%, respectively.

Data

Animal Data

Carfilzomib administered intravenously to pregnant rats and rabbits during the period of organogenesis was not teratogenic at doses up to 2 mg/kg/day in rats and 0.8 mg/kg/day in rabbits. Carfilzomib was not teratogenic at any dose tested. In rabbits, there was an increase in pre-implantation loss at ≥ 0.4 mg/kg/day and an increase in early resorptions and post-implantation loss and a decrease in fetal weight at the maternally toxic dose of 0.8 mg/kg/day. The doses of 0.4 and 0.8 mg/kg/day in rabbits are approximately 20% and 40%, respectively, of the recommended dose in humans of 27 mg/m^2 based on body surface area.

8.2 Lactation

Risk Summary

There is no information regarding the presence of Kyprolis in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Kyprolis and any potential adverse effects on the breastfed infant from Kyprolis or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

Kyprolis can cause fetal harm when administered to pregnant women [*see Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception measures to prevent pregnancy during treatment with Kyprolis and for at least 2 weeks following completion of therapy.

8.4 Pediatric Use

The safety and effectiveness of Kyprolis in pediatric patients have not been established.

8.5 Geriatric Use

Of 598 patients treated with Kyprolis monotherapy, 293 patients (49%) were ≥ 65 years of age and 96 patients (16%) were ≥ 75 years of age. The median age was 64 years. The incidence of serious adverse events was 44% in patients ≤ 65 years of age, 55% in patients 65 to 74 years of age, and 56% in patients ≥ 75 years of age [*see Warnings and Precautions - Cardiac Toxicities (5.1)*]. In Study 2 (n = 266), no overall differences in effectiveness were observed between these and younger patients.

Of 392 patients treated with Kyprolis in combination with lenalidomide and dexamethasone, 185 patients (47%) were ≥ 65 years of age and 43 patients (11%) were ≥75 years of age. The median age was 64 years. No overall differences in effectiveness were observed between these and younger patients. The incidence of serious adverse events was 50% in patients ≤ 65 years of age, 70% in patients 65 to 74 years of age, and 74% in patients ≥ 75 years of age [*see Warnings and Precautions - Cardiac Toxicities (5.1)*].

8.6 Renal Impairment

No starting dose adjustment is required in patients with baseline mild, moderate, or severe renal impairment or patients on chronic dialysis. The pharmacokinetics and safety of Kyprolis were evaluated in a Phase 2 trial in patients with normal renal function and those with mild, moderate, and severe renal impairment and patients on chronic dialysis. In this study, the pharmacokinetics of Kyprolis was not influenced by the degree of baseline renal impairment, including the patients on dialysis. Since dialysis clearance of Kyprolis

concentrations has not been studied, the drug should be administered after the dialysis procedure [*see Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

The safety, efficacy and pharmacokinetics of Kyprolis have not been evaluated in patients with baseline hepatic impairment. Patients with the following laboratory values were excluded from the Kyprolis clinical trials: ALT/AST ≥ 3 × upper limit of normal (ULN) and bilirubin ≥ 2 × ULN [*see Clinical Pharmacology (12.3)*].

8.8 Cardiac Impairment

Patients with New York Heart Association Class III and IV heart failure or recent myocardial infarction (within 3 to 6 months in different protocols) were not eligible for the clinical trials. Safety in this population has not been evaluated.

10 OVERDOSAGE

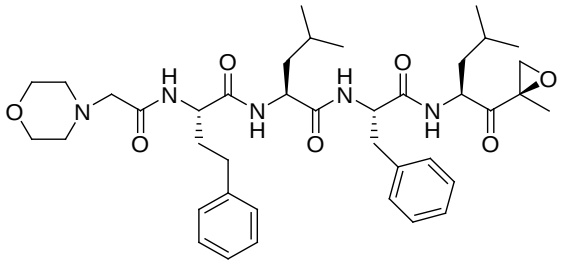
Acute onset of chills, hypotension, renal insufficiency, thrombocytopenia, and lymphopenia has been reported following a dose of 200 mg of Kyprolis administered in error.

There is no known specific antidote for Kyprolis overdosage. In the event of overdose, the patient should be monitored, specifically for the side effects and/or adverse reactions listed in *Adverse Reactions (6)*.

11 DESCRIPTION

Kyprolis (carfilzomib) is an antineoplastic agent available for intravenous use only. Kyprolisis a sterile, white to off-white lyophilized powder and is available as a single-dose vial. Each vial of Kyproliscontains 60 mg of carfilzomib, 3000 mg sulfobutyl ether beta-cyclodextrin, 57.7 mg citric acid, and sodium hydroxide for pH adjustment (target pH 3.5).

Carfilzomib is a modified tetrapeptidyl epoxide, isolated as the crystalline free base. The chemical name for carfilzomib is (2S)-N-((S)-1-((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2-ylcarbamoyl)-2-phenylethyl)-2-((S)-2-(2-morpholinoacetamido)-4-phenylbutanamido)-4-methylpentanamide. Carfilzomib has the following structure:



Carfilzomib is a crystalline substance with a molecular weight of 719.9. The molecular formula is $C_{40}H_{57}N_5O_7$. Carfilzomib is practically insoluble in water, and very slightly soluble in acidic conditions.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Carfilzomib is a tetrapeptide epoxyketone proteasome inhibitor that irreversibly binds to the N-terminal threonine-containing active sites of the 20S proteasome, the proteolytic core particle within the 26S proteasome. Carfilzomib had antiproliferative and proapoptotic activities in vitro in solid and hematologic tumor cells. In animals, carfilzomib inhibited proteasome activity in blood and tissue and delayed tumor growth in models of multiple myeloma, hematologic, and solid tumors.

12.2 Pharmacodynamics

Intravenous carfilzomib administration resulted in suppression of proteasome chymotrypsin-like (CT-L) activity when measured in blood 1 hour after the first dose. Doses of carfilzomib $\geq$ 15 mg/m^2 with or without lenalidomide and dexamethasone induced a $\geq$ 80% inhibition of the CT-L activity of the proteasome . In addition, carfilzomib, 20 mg/m^2 intravenously as a single agent, resulted in a mean inhibition of the low molecular mass polypeptide 2 (LMP2) and multicatalytic endopeptidase complex-like 1 (MECL1) subunits of the proteasome ranging from 26% to 32% and 41% to 49%, respectively. Proteasome inhibition was maintained for $\geq$ 48 hours following the first dose of carfilzomib for each week of dosing.

12.3 Pharmacokinetics

The C_{max} and AUC following a single intravenous dose of 27 mg/m^2 was 4232 ng/mL and 379 ng•hr/mL, respectively. Following repeated doses of carfilzomib at 15 and 20 mg/m^2, systemic exposure (AUC) and half-life were similar on Days 1 and 15 or 16 of Cycle 1, suggesting there was no systemic carfilzomib accumulation. At doses between 20 and 36 mg/m^2, there was a dose-dependent increase in exposure.

Distribution: The mean steady-state volume of distribution of a 20 mg/m^2 dose of carfilzomib was 28 L. When tested *in vitro*, the binding of carfilzomib to human plasma proteins averaged 97% over the concentration range of 0.4 to 4 micromolar.

Metabolism: Carfilzomib was rapidly and extensively metabolized. The predominant metabolites measured in human plasma and urine, and generated *in vitro* by human hepatocytes, were peptide fragments and the diol of carfilzomib, suggesting that peptidase cleavage and epoxide hydrolysis were the principal pathways of metabolism. Cytochrome P450-mediated mechanisms played a minor role in overall carfilzomib metabolism. The metabolites have no known biologic activity.

Elimination: Following intravenous administration of doses ≥ 15 mg/m^2, carfilzomib was rapidly cleared from the systemic circulation with a half-life of ≤ 1 hour on Day 1 of Cycle 1. The systemic clearance ranged from 151 to 263 L/hour, and exceeded hepatic blood flow, suggesting that carfilzomib was largely cleared extrahepatically. In 24 hours, approximately 25% of the administered dose of carfilzomib was excreted in urine as metabolites. Urinary and fecal excretion of the parent compound was negligible (0.3% of total dose).

Age: Population pharmacokinetic analyses that included patients ranging from 35 to 87.6 years of age indicate that the pharmacokinetics of carfilzomib are not influenced by age.

Gender: Population pharmacokinetic analyses indicate that the pharmacokinetics of carfilzomib are not influenced by gender.

Hepatic Impairment: No dedicated studies have been completed in patients with hepatic impairment.

Renal Impairment: A pharmacokinetic study was conducted in which 50 multiple myeloma patients who had various degrees of renal impairment and who were classified according to their creatinine clearances (CLcr) into the following groups: normal function (CLcr > 80 mL/min, n = 12), mild impairment (CLcr 50–80 mL/min, n = 12), moderate impairment (CLcr 30–49 mL/min, n =10), severe impairment (CLcr < 30 mL/min, n = 8), and chronic dialysis (n = 8). Kyprolis, as a single agent, was administered intravenously over 2 to 10 minutes, on two consecutive days, weekly for three weeks (Days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest period every 28 days. Patients received an initial dose of 15 mg/m^2, which could be escalated to 20 mg/m^2 starting in Cycle 2 if 15 mg/m^2 was well tolerated in Cycle 1. In this study, renal function status had no effect on the clearance or exposure of carfilzomib following a single or repeat-dose administration [*see Use in Specific Populations (8.6)*].

Cytochrome P450: In an *in vitro* study using human liver microsomes, carfilzomib showed modest direct (Ki = 1.7 micromolar) and time-dependent inhibition (Ki = 11 micromolar) of human cytochrome CYP3A4/5. In vitro studies indicated that carfilzomib did not induce human CYP1A2 and CYP3A4 in cultured fresh human hepatocytes. Cytochrome P450-mediated mechanisms play a minor role in the overall metabolism of carfilzomib. A clinical trial of 17 patients using oral midazolam as a CYP3A probe demonstrated that the pharmacokinetics of midazolam were unaffected by concomitant carfilzomib administration. Kyprolis is not expected to inhibit CYP3A4/5 activities and/or affect the exposure to CYP3A4/5 substrates.

P-gp: Carfilzomib is a P-glycoprotein (P-gp) substrate. In vitro, carfilzomib inhibited the efflux transport of P-gp substrate digoxin by 25% in a Caco-2 monolayer system. However, given that Kyprolis is administered intravenously and is extensively metabolized, the pharmacokinetics of Kyprolis is unlikely to be affected by P-gp inhibitors or inducers.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with carfilzomib.

Carfilzomib was clastogenic in the *in vitro* chromosomal aberration test in peripheral blood lymphocytes. Carfilzomib was not mutagenic in the *in vitro* bacterial reverse mutation (Ames) test and was not clastogenic in the *in vivo* mouse bone marrow micronucleus assay.

Fertility studies with carfilzomib have not been conducted. No effects on reproductive tissues were noted during 28-day repeat-dose rat and monkey toxicity studies or in 6-month rat and 9-month monkey chronic toxicity studies.

13.2 Animal Toxicology and/or Pharmacology

Monkeys administered a single bolus intravenous dose of carfilzomib at 3 mg/kg (approximately 1.3 times recommended dose in humans of 27 mg/m^2 based on body surface area) experienced hypotension, increased heart rate, and increased serum levels of troponin-T. The repeated bolus intravenous administration of carfilzomib at ≥ 2 mg/kg/dose in rats and 2 mg/kg/dose in monkeys using dosing schedules similar to those used clinically resulted in mortalities that were due to toxicities occurring in the cardiovascular (cardiac failure, cardiac fibrosis, pericardial fluid accumulation, cardiac hemorrhage/degeneration), gastrointestinal (necrosis/hemorrhage), renal (glomerulonephropathy, tubular necrosis, dysfunction), and pulmonary (hemorrhage/inflammation) systems. The dose of 2 mg/kg/dose in rats is approximately half the recommended dose in humans of 27 mg/m^2 based on body surface area. The dose of 2 mg/kg/dose in monkeys is approximately equivalent to the recommended dose in humans based on body surface area.

14 CLINICAL STUDIES

14.1 In Combination with Lenalidomide and Dexamethasone for the treatment of Patients with Relapsed Multiple Myeloma

Study 1 was a randomized, open-label, multicenter study which evaluated the combination of Kyprolis with lenalidomide and low-dose dexamethasone (KRd) versus lenalidomide and low-dose dexamethasone alone (Rd) in patients with relapsed multiple myeloma who had received 1 to 3 prior lines of therapy. (A line of therapy is a planned course of treatment (including sequential induction, transplantation, consolidation and/or maintenance) without an interruption for lack of efficacy, such as for relapse or progressive disease.) Patients who had the following were excluded from the trial: refractory to bortezomib in the most recent

regimen, refractory to lenalidomide and dexamethasone in the most recent regimen, creatinine clearance rates < 50 mL/min, New York Heart Association Class III to IV congestive heart failure, or myocardial infarction within the last 4 months. Kyprolis treatment was administered for a maximum of 18 cycles unless discontinued early for disease progression or unacceptable toxicity. Lenalidomide and dexamethasone administration could continue until progression or unacceptable toxicity.

The 792 patients in Study 1 were randomized 1:1 to the KRd or Rd arm. The demographics and baseline characteristics were well-balanced between the two arms (see Table 9). Only 53% of the patients had testing for genetic mutations; a high-risk genetic mutation was identified for 12% of patients in the KRd arm and in 13% in the Rd arm.

Table 9: Demographics and Baseline Disease Characteristics in Study 1 (Combination Therapy for Relapsed Multiple Myeloma)

Characteristic	KRd Combination Therapy	
	KRd Arm (N = 396)	Rd Arm (N = 396)
Age, Median Years (min, max)	64.0 (38, 87)	65.0 (31, 91)
Age Group, ≥ 75 Years, n (%)	43 (11)	53 (13)
Males, n (%)	215 (54)	232 (59)
Race, n (%)		
White	377 (95)	377 (95)
Black	12 (3)	11 (3)
Other[a]	7 (2)	8 (2)
Number of Prior Regimens		
1	184 (46%)	157 (40%)
2	120 (30%)	139 (35%)
3[b]	92 (23%)	100 (25%)
Prior Transplantation	217 (55%)	229 (58%)
ECOG		
0	165 (42)	175 (44)
1	191 (48)	186 (47)
2	40 (10)	35 (9)
ISS Stage at study baseline, n (%)		
I	167 (42%)	154 (39%)
II	148 (37%)	152 (38%)
III	73 (18%)	82 (21%)
CrCL, mL/min Median (min, max)	78.6 (38.7, 211.9)	79.2 (30.0, 207.8)
30 to < 50, n (%)	19 (5)	32 (8)
50 to < 80, n (%)	185 (47)	170 (43)
Refractory to Last Therapy, n (%)	(28%)	(30%)
Refractory at any time to (%):		
Bortezomib	(15%)	(15%)
Lenalidomide	(7%)	(7%)
Bortezomib + IMiD	(6%)	(7%)

ECOG PS = Eastern Cooperative Oncology Group Performance Status; CrCL= creatinine clearance; IgG = immunoglobulin G; IMID = immunomodulators; ISS = International Staging System; KRd = Kyprolis, lenalidomide, and low-dose dexamethasone; Rd = lenalidomide and low-dose dexamethasone

[a] Includes Other, Asian/Native Hawaiian/Other Pacific Islander, or American Indian or Alaska Native.

[b] Including 2 patients with 4 prior regimens.

Patients in the Kyprolis, Revlimid (lenalidomide), and low-dose dexamethasone (KRd) arm demonstrated improved progression-free survival (PFS) compared with those in the lenalidomide and low-dose dexamethasone (Rd) arm (HR = 0.69, with 2-sided p-value = 0.0001) as determined using standard objective International Myeloma Working Group (IMWG)/European Blood and Marrow Transplantation (EBMT) response criteria by an Independent Review Committee (IRC).

The median PFS was 26.3 months (95% CI: 23.3 to 30.5 months) in the KRd arm vs. 17.6 months (95% CI: 15.0 to 20.6 months) in the lenalidomide and low-dose dexamethasone (Rd) arm (seeTable 10).

The results of overall survival (OS) were not significantly different at the interim analysis (Figure 2).

Table 10: Efficacy Outcomes in Study 1 (Combination Therapy for Relapsed Multiple Myeloma)

	KRd Combination Therapy	
	KRd Arm[a] (N = 396)	**Rd Arm[a] (N = 396)**
PFS Months Median (95% CI)	26.3 (23.3, 30.5)	17.6 (15.0, 20.6)
HR (95% CI); 2-sided p-value[b]	0.69 (0.57, 0.83); 0.0001	
ORR n (%)	345 (87)	264 (67)
sCR	56 (14)	17 (4)
CR	70 (18)	20 (5)
VGPR	151 (38)	123 (31)
PR	68 (17)	104 (26)

CI = confidence interval; CR = complete response; EBMT = European Blood and Marrow Transplantation; IMWG = International Myeloma Working Group; KRd = Kyprolis, lenalidomide, and low-dose dexamethasone; ORR = overall response rate; PFS = progression-free survival; Rd = lenalidomide and low-dose dexamethasone; sCR = stringent complete response; VGPR = very good partial response

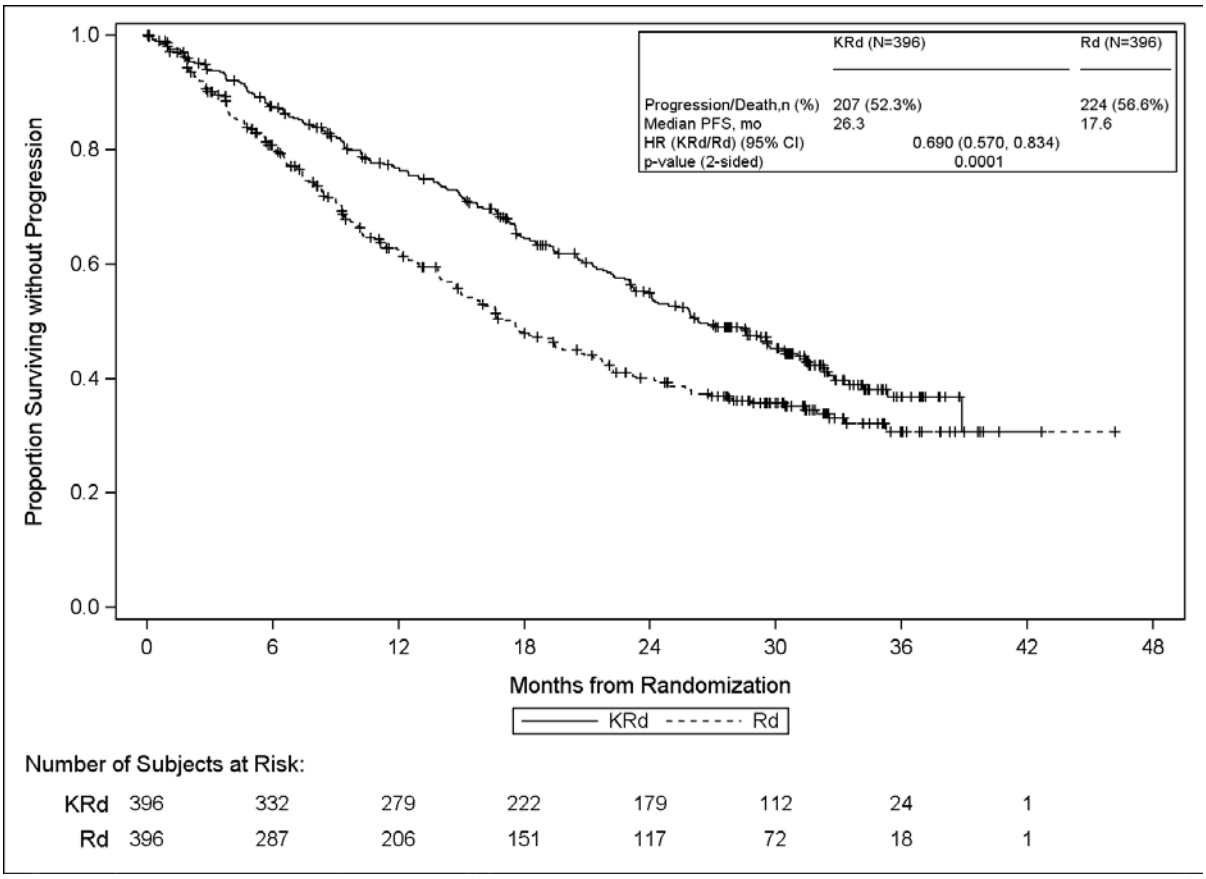
[a] As determined by an Independent Review Committee using standard objective IMWG/EBMT response criteria.

[b] Statistically significant.

The median duration of response was 28.6 months (95% CI: 24.9 to 31.3 months) for the 345 patients achieving a response in the KRd arm and 21.2 months (95% CI: 16.7 to 25.8 months) for the 264 patients achieving a response in the Rd arm. The median time to

response was 1 month (range 1 to 14 months) in the KRd arm and 1 month (range 1 to 16 months) in the Rd arm.

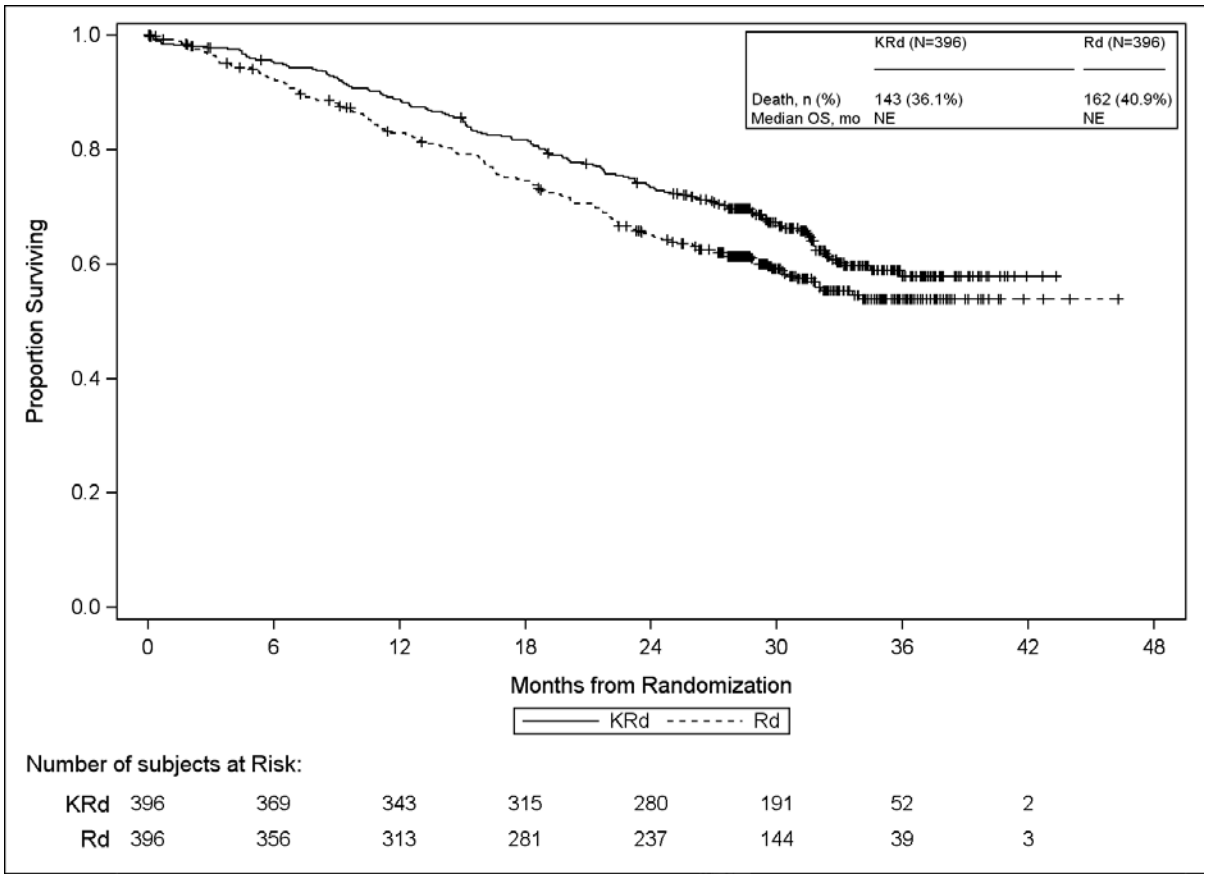
Figure 1: Kaplan-Meier Curve of Progression-Free Survival in Relapsed Multiple Myeloma in Study 1



CI = confidence interval; EBMT = European Blood and Marrow Transplantation; HR = hazard ratio; IMWG = International Myeloma Working Group; KRd = Kyprolis, lenalidomide, and low-dose dexamethasone; mo = months; PFS = progression-free survival; Rd = lenalidomide and low-dose dexamethasone arm

Note: The response and PD outcomes were determined using standard objective IMWG/EBMT response criteria.

Figure 2: Kaplan-Meier Curve of Interim Overall Survival in Relapsed Multiple Myeloma in Study 1



KRd = Kyprolis, lenalidomide, and low-dose dexamethasone; NE = not estimable; OS = overall survival; PFS = progression-free survival; Rd = lenalidomide and low-dose dexamethasone arm
Note: The interim OS analysis did not meet the protocol-specified early stopping boundary for OS.

14.2 Monotherapy for Treatment of Patients with Relapsed and Refractory Multiple Myeloma

Study 2 was a single-arm, multicenter clinical trial of Kyprolis monotherapy. Eligible patients were those with relapsed multiple myeloma who had received at least two prior therapies (including bortezomib and thalidomide and/or lenalidomide) and had less than or equal to 25% response to the most recent therapy or had disease progression during or within 60 days of the most recent therapy. Patients were excluded from the trial if they were refractory to all prior therapies, or with total bilirubin levels ≥ 2 × upper limit of normal (ULN); creatinine clearance rates < 30 mL/min; New York Heart Association Class III to IV congestive heart failure; symptomatic cardiac ischemia; myocardial infarction within the last

6 months; peripheral neuropathy Grade 3 or 4, or peripheral neuropathy Grade 2 with pain; active infections requiring treatment; or pleural effusion.

Kyprolis was administered intravenously over 2 to 10 minutes on two consecutive days each week for three weeks, followed by a 12-day rest period (28-day treatment cycle), until disease progression, unacceptable toxicity, or for a maximum of 12 cycles. Patients received 20 mg/m^2 at each dose in Cycle 1, and 27 mg/m^2 in subsequent cycles. Dexamethasone 4 mg orally or intravenously was administered prior to Kyprolis doses in the first and second cycles.

A total of 266 patients were enrolled. Baseline patient and disease characteristics are summarized in Table 11.

Table 11: Demographics and Baseline Disease Characteristics in Study 2 (Monotherapy for Relapsed and Refractory Multiple Myeloma)

Characteristic	Number of Patients (%)
Patient Characteristics	
Enrolled patients	266 (100)
Median age, years (range)	63.0 (37, 87)
Age group, < 65 / ≥ 65 (years)	146 (55) / 120 (45)
Gender (male / female)	155 (58) / 111 (42)
Race (White / Black / Asian / Other)	190 (71) / 53 (20) / 6 (2) / 17 (6)
Disease Characteristics	
Number of Prior Regimens (median)	5[a]
Prior Transplantation	198 (74)
Refractory Status to Most Recent Therapy[b]	
Refractory: Progression during most recent therapy	198 (74)
Refractory: Progression within 60 days after completion of most recent therapy	38 (14)
Refractory: ≤ 25% response to treatment	16 (6)
Relapsed: Progression after 60 days post treatment	14 (5)
Years since diagnosis, median (range)	5.35 (0.5, 22.3)
Plasma cell involvement (< 50% / ≥ 50% / unknown or missing)	143 (54) / 106 (40) / 17 (6)
ISS, n (%)	
I	76 (29)
II	102 (38)
III	81 (31)

Cytogenetics or FISH analyses	
Normal/Favorable	159 (60)
Poor Prognosis	75 (28)
Unknown/Not tested	32 (12)
Creatinine clearance < 30 (mL/min)	6 (2)

[a] Range: 1, 20.
[b] Categories for refractory status are derived by programmatic assessment using available laboratory data.

The median number of cycles started was four.

The primary endpoint was the overall response rate (ORR) as determined by Independent Review Committee assessment using International Myeloma Working Group criteria. The ORR (stringent complete response [sCR] + complete response [CR] + very good partial response [VGPR] + partial response [PR]) was 22.9% (95% CI: 18.0, 28.5) (N = 266) (see Table 12). The median duration of response (DOR) was 7.8 months (95% CI: 5.6, 9.2).

Table 12: Response Categories

Characteristic	Study Patients n (%)
Number of Patients (%)	266 (100)
Response Category[a]	
Complete Response	1 (0)
Very Good Partial Response	13 (5)
Partial Response	47 (18)
Overall Response	61 (23)
95% CI[b]	(18.0, 28.5)

[a] As assessed by the Independent Review Committee.
[b] Exact confidence interval.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Kyprolis (carfilzomib) is supplied as an individually cartoned single-dose vial containing a dose of 60 mg of carfilzomib as a white to off-white lyophilized cake or powder.

- NDC 76075-101-01, 60 mg carfilzomib per vial

16.2 Storage and Handling

Unopened vials should be stored refrigerated (2°C to 8°C; 36°F to 46°F). Retain in original package to protect from light.

17 PATIENT COUNSELING INFORMATION

Discuss the following with patients prior to treatment with Kyprolis:

Instruct patients to contact their physician if they develop any of the following symptoms: fever, chills, rigors, chest pain, cough, or swelling of the feet or legs, bleeding, bruising, weakness, headaches, confusion, seizures, or visual loss.

Advise patients that Kyprolis may cause fatigue, dizziness, fainting, and/or drop in blood pressure. Advise patients not to drive or operate machinery if they experience any of these symptoms.

Advise patients that they may experience shortness of breath (dyspnea) during treatment with Kyprolis. This most commonly occurs within a day of dosing. Advise patients to contact their physicians if they experience shortness of breath.

Counsel patients to avoid dehydration, since patients receiving Kyprolis therapy may experience vomiting and/or diarrhea. Instruct patients to seek medical advice if they experience symptoms of dizziness, lightheadedness, or fainting spells.

Counsel females of reproductive potential to use effective contraceptive measures to prevent pregnancy during treatment with Kyprolis. Advise the patient that if she becomes pregnant during treatment, to contact her physician immediately. Advise patients not to take Kyprolis

treatment while pregnant or breastfeeding. If a patient wishes to restart breastfeeding after treatment, advise her to discuss the appropriate timing with her physician.

Advise patients to discuss with their physician any medication they are currently taking prior to starting treatment with Kyprolis, or prior to starting any new medication(s) during treatment with Kyprolis.

Manufactured for:
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U.S. Patent Numbers: http://pat.amgen.com/kyprolis

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