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)	01/2016
Dosage and Administration (2)	06/2016
Warnings and Precautions (5)	08/2016

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

Kyprolis is a proteasome inhibitor that is indicated:

- in combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy. (1, 14)
- as a single agent for the treatment of patients with relapsed or refractory multiple myeloma who have received one or more lines of therapy. (1, 14)

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

- See Full Prescribing Information for dosing.
- Hydrate prior to and following Kyprolis administration as needed. (2.1)
- Premedicate Kyprolis infusions with dexamethasone prior to all Cycle 1 doses and if infusion reaction symptoms develop or reappear. (2.1)
- Administer the 20/56 mg/m^2 regimen by 30-minute infusion and the 20/27 mg/m^2 regimen by 10-minute infusion. (2.2)

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

For injection: 30 mg or 60 mg, lyophilized powder in single-dose vial for reconstitution (3)

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

None (4)

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

- Cardiac Toxicities: Monitor for signs and symptoms of cardiac failure or 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 controlled, interrupt treatment with Kyprolis. (5.7)
- Venous Thrombosis: Thromboprophylaxis is recommended. (5.8)
- Infusion Reactions: Premedicate with dexamethasone. (2.1, 5.9)
- Hemorrhage: Fatal or serious cases of hemorrhage may occur, including gastrointestinal, pulmonary, and intracranial hemorrhage. Promptly evaluate signs and symptoms of blood loss. (5.10)
- Thrombocytopenia: Monitor platelet counts; interrupt or reduce Kyprolis dosing as clinically indicated. (2.3, 5.11)
- Hepatic Toxicity and Hepatic Failure: Monitor liver enzymes regularly. Withhold Kyprolis if suspected. (5.12)
- Thrombotic Microangiopathy: Monitor for signs and symptoms. Discontinue Kyprolis if suspected. (5.13)
- Posterior Reversible Encephalopathy Syndrome (PRES): Consider neuro-radiological imaging (MRI) for onset of visual or neurological symptoms; discontinue Kyprolis if suspected. (5.14)
- Embryo-Fetal Toxicity: Kyprolis can cause fetal harm. Females of reproductive potential should avoid becoming pregnant while being treated. (5.15, 8.1)

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

The most common adverse reactions occurring in at least 20% of patients treated with Kyprolis in monotherapy trials: anemia, fatigue, thrombocytopenia, nausea, pyrexia, dyspnea, diarrhea, headache, cough, edema peripheral. (6)

The most common adverse reactions occurring in at least 20% of patients treated with Kyprolis in the combination therapy trials: anemia, neutropenia, diarrhea, dyspnea, fatigue, thrombocytopenia, pyrexia, insomnia, muscle spasm, cough, upper respiratory tract infection, hypokalemia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Medical Information at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

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

- Geriatric use: 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: 08/2016

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Relapsed or Refractory Multiple Myeloma

- Kyprolis is indicated in combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy *[see Clinical Studies (14.1)]*.
- Kyprolis is indicated as a single agent for the treatment of patients with relapsed or refractory multiple myeloma who have received one or more lines of therapy *[see Clinical Studies (14.2, 14.3)]*.

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)]*.
- **Electrolyte Monitoring** - Monitor serum potassium levels regularly during treatment with Kyprolis.
- **Premedications** - Premedicate with the recommended dose of dexamethasone for monotherapy or the recommended dexamethasone dose if on combination therapy *[see Dosage and Administration (2.2)]*. Administer dexamethasone 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 (5.9)]*. Reinstate dexamethasone premedication if these symptoms occur during subsequent cycles.

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- **Administration** - Infuse over 10 or 30 minutes depending on the Kyprolis dose regimen *[see Dosage and Administration (2.2)]*. 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. In patients with a body surface area greater than 2.2 m^2, calculate the 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 with dexamethasone or with lenalidomide plus 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 for patients being treated with Kyprolis to decrease the risk of herpes zoster reactivation.

2.2 Recommended Dosing

<u>Kyprolis in Combination with Lenalidomide and Dexamethasone</u>

For the combination regimen with lenalidomide and dexamethasone, 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 the dose to 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.

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Table 1: Kyprolis (10-Minute Infusion) 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 (mg)	40	-	-	40	-	-	40	-	-	40	-
Lenalidomide	25 mg daily on Days 1-21									-	-
	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 (mg)	40	-	-	40	-	-	40	-	-	40	-
Lenalidomide	25 mg daily on Days 1-21									-	-
	Cycles 13 and later[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 (mg)	40	-	-	40	-	-	40	-	-	40	-
Lenalidomide	25 mg daily on Days 1-21									-	-

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

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Continue treatment until disease progression or unacceptable toxicity occurs *[see Dosage and Administration (2.3)]*. 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 in Combination with Dexamethasone

For the combination regimen with dexamethasone, administer Kyprolis intravenously as a 30-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. Administer Kyprolis by 30-minute infusion at a starting dose of 20 mg/m^2 in Cycle 1 on Days 1 and 2. If tolerated, escalate the dose to 56 mg/m^2 on Day 8 of Cycle 1. Dexamethasone 20 mg is taken by mouth or intravenously on Days 1, 2, 8, 9, 15, 16, 22, and 23 of each 28-day cycle. Administer dexamethasone 30 minutes to 4 hours before Kyprolis.

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Table 2: Kyprolis (30-Minute Infusion) in Combination with 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	Day 23	Days 24-28
Kyprolis (mg/m^2)	20	20	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)	20	20	-	20	20	-	20	20	-	20	20	-
	Cycles 2 and later											
	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	Day 23	Days 24-28
Kyprolis (mg/m^2)	56	56	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)	20	20	-	20	20	-	20	20	-	20	20	-

Treatment may be continued until disease progression or unacceptable toxicity occurs *[see Dosage and Administration (2.3)]*. Refer to the dexamethasone Prescribing Information for other concomitant medications.

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Kyprolis Monotherapy

For monotherapy, administer Kyprolis intravenously as a 10-minute or 30-minute infusion depending on the regimen as described below.

20/27 mg/m^2 regimen by 10-minute infusion

For monotherapy using the 20/27 mg/m^2 regimen, administer Kyprolis intravenously as a 10-minute infusion *[see Clinical Studies (14.3)]*. In Cycles 1 through 12, administer Kyprolis on two consecutive days, each week for three weeks followed by a 12-day rest period as shown in Table 3. Each 28-day period is considered one treatment cycle. From Cycle 13, omit the Day 8 and 9 doses of Kyprolis (see Table 3). Premedicate with dexamethasone 4 mg orally or intravenously 30 minutes to 4 hours before each Kyprolis dose in Cycle 1, then as needed to help prevent infusion reactions *[see Dosage and Administration (2.1)]*. The recommended starting dose of Kyprolis is 20 mg/m^2 in Cycle 1 on Days 1 and 2. If tolerated, escalate the dose to 27 mg/m^2 on Day 8 of Cycle 1. Treatment may continue until disease progression or unacceptable toxicity occurs.

Table 3: Kyprolis Monotherapy (10-Minute Infusion)

	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)[a]	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 and later									
	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	-	-

[a] Dexamethasone premedication is required for each Kyprolis dose in Cycle 1.

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20/56 mg/m^2 regimen by 30-minute infusion

For monotherapy using the 20/56 mg/m^2 regimen, administer Kyprolis intravenously as a 30-minute infusion *[see Clinical Studies (14.3)]*. In Cycles 1 through 12, administer Kyprolis on two consecutive days, each week for three weeks followed by a 12-day rest period as shown in Table 4. Each 28-day period is considered one treatment cycle. From Cycle 13, omit the Day 8 and 9 doses of Kyprolis (see Table 4). Premedicate with dexamethasone 8 mg orally or intravenously 30 minutes to 4 hours before each Kyprolis dose in Cycle 1, then as needed to help prevent infusion reactions *[see Dosage and Administration (2.1)]*. The recommended starting dose of Kyprolis is 20 mg/m^2 in Cycle 1 on Days 1 and 2. If tolerated, escalate the dose to 56 mg/m^2 on Day 8 of Cycle 1. Treatment may continue until disease progression or unacceptable toxicity occurs.

Table 4: Kyprolis Monotherapy (30-Minute Infusion)

	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)[a]	20	20	-	56	56	-	56	56	-	-
	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)	56	56	-	56	56	-	56	56	-	-
	Cycles 13 and later									
	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)	56	56	-	-	-	-	56	56	-	-

[a] Dexamethasone premedication is required for each Kyprolis dose in Cycle 1.

2.3 Dose Modifications Based on Toxicities

Modify dosing based on toxicity. Recommended actions and dose modifications for Kyprolis are presented in Table 5. Dose level reductions are presented in Table 6. See the lenalidomide and dexamethasone Prescribing Information respectively for dosing recommendations.

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Table 5: Dose Modifications for Toxicity[a] during Kyprolis Treatment

Hematologic Toxicity	Recommended Action
• ANC less than 0.5×10^9/L	• Withhold dose • If recovered to greater than or equal to 0.5×10^9/L, continue at the same dose level • For subsequent drops to less than 0.5×10^9/L, follow the same recommendations as above and consider 1 dose level reduction when restarting Kyprolis[a]
• Febrile neutropenia ANC less than 0.5×10^9/L and an oral temperature more than 38.5°C or two consecutive readings of more than 38.0°C for 2 hours	• Withhold dose • If ANC returns to baseline grade and fever resolves, resume at the same dose level

• Platelets less than 10×10^9/L or evidence of bleeding with thrombocytopenia
[see Warnings and Precautions (5)]
	• Withhold dose
	  • If recovered to greater than or equal to 10×10^9/L and/or bleeding is controlled, continue at the same dose level
	  • For subsequent drops to less than 10×10^9/L, follow the same recommendations as above and consider 1 dose level reduction when restarting Kyprolis[a]

Renal Toxicity	**Recommended Action**

• Serum creatinine greater than or equal to 2 × baseline, or
• Creatinine clearance less than 15 mL/min, or creatinine clearance decreases to less than or equal 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]

ANC = absolute neutrophil count
[a] See Table 6 for dose level reductions.
[b] CTCAE Grades 3 and 4.

Table 6: Dose Level Reductions for Kyprolis

Regimen	Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
Kyprolis, Lenalidomide, and Dexamethasone, or Monotherapy (20/27 mg/m^2)	27 mg/m^2	20 mg/m^2	15 mg/m^2[a]	—
Kyprolis and Dexamethasone, or Monotherapy (20/56 mg/m^2)	56 mg/m^2	45 mg/m^2	36 mg/m^2	27 mg/m^2[a]

Note: Infusion times remain unchanged during dose reduction(s).
[a] If toxicity persists, discontinue Kyprolis treatment.

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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.

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.

<u>Reconstitution/Preparation Steps:</u>

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%.
3. Aseptically reconstitute each vial by slowly injecting **29 mL** (for 60 mg vial) or **15 mL** (for 30 mg vial) Sterile Water for Injection, USP, through the stopper and directing the solution onto the INSIDE WALL OF THE VIAL to minimize foaming.

4. 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.
5. 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.
6. Discard any unused portion left in the vial. DO NOT pool unused portions from the vials. DO NOT administer more than one dose from a vial.
7. Optionally, Kyprolis can be administered in an intravenous bag.

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8. When administering in an intravenous bag, withdraw the calculated dose *[see Dosage and Administration (2)]* from the vial and dilute into 50 mL or 100 mL intravenous bag containing 5% Dextrose Injection, USP (based on the calculated total dose and infusion time).

The stabilities of reconstituted Kyprolis under various temperature and container conditions are shown in Table 7.

Table 7: Stability of Reconstituted Kyprolis

Storage Conditions of Reconstituted Kyprolis	Stability[a] per Container		
	Vial	Syringe	Intravenous 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 is supplied as follows:

- For injection: 30 mg lyophilized cake or powder in single-dose vial for reconstitution
- For injection: 60 mg lyophilized cake or powder in single-dose vial for reconstitution

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. Some events occurred in patients with normal baseline ventricular function. In clinical studies with Kyprolis, these events occurred throughout the course of Kyprolis therapy. Death due to cardiac arrest has occurred within one day of Kyprolis administration. In a randomized, open-label, multicenter trial evaluating Kyprolis

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in combination with lenalidomide and dexamethasone (KRd) *versus* lenalidomide/dexamethasone (Rd), the incidence of cardiac failure events was 6% in the KRd arm *versus* 4% in the Rd arm. In a randomized, open-label, multicenter trial of Kyprolis plus dexamethasone (Kd) *versus* bortezomib plus dexamethasone (Vd), the incidence of cardiac failure events was 8% in the Kd arm *versus* 3% in the Vd arm.

Monitor patients for clinical signs or symptoms of cardiac failure or cardiac ischemia. Evaluate promptly if cardiac toxicity is suspected. Withhold Kyprolis for Grade 3 or 4 cardiac adverse events until recovery, and consider whether to restart Kyprolis at 1 dose level reduction based on a benefit/risk assessment *[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 compared to patients < 75 years of age. Patients with New York Heart Association Class III and IV heart failure, recent myocardial infarction, conduction abnormalities, angina, or arrhythmias uncontrolled by medications were not eligible for the clinical trials. These patients may be at greater risk for cardiac complications and should have a comprehensive medical assessment (including blood pressure and fluid management) prior to starting treatment with Kyprolis and remain under close follow-up *[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 (including renal failure) have occurred in approximately 10% of patients treated with Kyprolis. 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)]*.

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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 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); Warnings and Precautions (5.1 and 5.4); and Adverse Reactions (6)]*.

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5.7 Hypertension

Hypertension, including hypertensive crisis and hypertensive emergency, has been observed with Kyprolis. In a randomized, open-label, multicenter trial evaluating Kyprolis in combination with KRd *versus* Rd, the incidence of hypertension events was 16% in the KRd arm *versus* 8% in the Rd arm. In a randomized, open-label, multicenter trial of Kd *versus* Vd, the incidence of hypertension events was 26% in the Kd arm *versus* 10% in the Vd arm. 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 a randomized, open-label, multicenter trial evaluating KRd *versus* Rd (with thromboprophylaxis used in both arms), the incidence of venous thromboembolic events in the first 12 cycles was 13% in the KRd arm *versus* 6% in the Rd arm. In a randomized, open-label, multicenter trial of Kd *versus* Vd, the incidence of venous thromboembolic events in months 1–6 was 9% in the Kd arm *versus* 2% in the Vd arm. With Kyprolis monotherapy, the incidence of venous thromboembolic events was 2%.

Thromboprophylaxis is recommended for patients being treated with the combination of Kyprolis with dexamethasone or with lenalidomide plus dexamethasone. The thromboprophylaxis regimen should be based on an assessment of the patient's underlying risks.

Patients using oral contraceptives or a hormonal method of contraception associated with a risk of thrombosis should consider an alternative method of effective contraception during treatment with Kyprolis in combination with dexamethasone or lenalidomide plus dexamethasone.

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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 Hemorrhage

Fatal or serious cases of hemorrhage have been reported in patients treated with Kyprolis. Hemorrhagic events have included gastrointestinal, pulmonary, and intracranial hemorrhage and epistaxis. The bleeding can be spontaneous, and intracranial hemorrhage has occurred without trauma. Hemorrhage has been reported in patients having either low or normal platelet counts. Hemorrhage has also been reported in patients who were not on antiplatelet therapy or anticoagulation. Promptly evaluate signs and symptoms of blood loss. Reduce or withhold dose as appropriate *[see Dosage and Administration (2) and Adverse Reactions (6)]*.

5.11 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)]*. Hemorrhage may occur *[see Adverse Reactions (6) and Warnings and Precautions (5.10)]*.

5.12 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

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regularly, regardless of baseline values. Reduce or withhold dose as appropriate *[see Dosage and Administration (2) and Adverse Reactions (6)]*.

5.13 Thrombotic Microangiopathy

Cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), have been reported in patients who received Kyprolis. Some of these events have been fatal. 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.

5.14 Posterior Reversible Encephalopathy Syndrome

Cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving Kyprolis. 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.

5.15 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.

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 *[see Use in Specific Populations (8.1, 8.3)]*.

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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 Renal Failure *[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 Thrombosis *[see Warnings and Precautions (5.8)]*
- Infusion Reactions *[see Warnings and Precautions (5.9)]*
- Hemorrhage *[see Warnings and Precautions (5.10)]*
- Thrombocytopenia *[see Warnings and Precautions (5.11)]*
- Hepatic Toxicity and Hepatic Failure *[see Warnings and Precautions (5.12)]*
- Thrombotic Microangiopathy *[see Warnings and Precautions (5.13)]*
- Posterior Reversible Encephalopathy Syndrome *[see Warnings and Precautions (5.14)]*

6.1 Clinical Trials 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.

<u>Safety Experience with Kyprolis in Combination with Lenalidomide and Dexamethasone in Patients with Multiple Myeloma</u>

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.

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Deaths due to adverse reactions 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 *versus* Rd) included cardiac 10 (3%) *versus* 7 (2%), infection 9 (2%) *versus* 10 (3%), renal 0 (0%) *versus* 1 (< 1%), and other adverse reactions 9 (2%) *versus* 10 (3%). Serious adverse reactions 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 reactions reported in the KRd arm as compared with the Rd arm were pneumonia (14% *versus* 11%), respiratory tract infection (4% *versus* 1.5%), pyrexia (4% *versus* 2%), and pulmonary embolism (3% *versus* 2%). Discontinuation due to any adverse reaction occurred in 26% in the KRd arm *versus* 25% in the Rd arm. Adverse reactions leading to discontinuation of Kyprolis occurred in 12% of patients and the most common reactions included pneumonia (1%), myocardial infarction (0.8%), and upper respiratory tract infection (0.8%).

Common Adverse Reactions (≥ 10%)

The adverse reactions in the first 12 cycles of therapy that occurred at a rate of 10% or greater in the KRd arm are presented in Table 8.

Table 8: Most Common Adverse Reactions (≥ 10% in the KRd Arm) Occurring in Cycles 1–12 (20/27 mg/m^2 Regimen In Combination with Lenalidomide and Dexamethasone)

	KRd Arm (N = 392) n (%)		**Rd Arm (N = 389) n (%)**	
Adverse Reactions by Body System	**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				

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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[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[c]	91 (23)	2 (1)	52 (13)	0
Dyspnea[d]	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[e]	49 (13)	16 (4)	22 (6)	9 (2)
Hypertension[f]	41 (11)	12 (3)	15 (4)	4 (1)

KRd = Kyprolis, lenalidomide, and dexamethasone; Rd = lenalidomide and dexamethasone

[a] Pneumonia includes pneumonia and bronchopneumonia.

[b] Peripheral neuropathies includes peripheral neuropathy, peripheral sensory neuropathy, and peripheral motor neuropathy.

[c] Cough includes cough and productive cough.

[d] Dyspnea includes dyspnea and dyspnea exertional.

[e] Embolic and thrombotic events, venous include deep vein thrombosis, pulmonary embolism, thrombophlebitis superficial, thrombophlebitis, venous thrombosis limb, post thrombotic syndrome, venous thrombosis.

[f] Hypertension includes hypertension, hypertensive crisis.

There were 274 (70%) patients in the KRd arm who received treatment beyond Cycle 12. There were no new clinically relevant adverse reactions that emerged in the later treatment cycles.

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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, pericardial effusion
- **Eye disorders:** cataract, vision blurred
- **Gastrointestinal disorders:** abdominal pain, abdominal pain upper, dyspepsia, gastrointestinal hemorrhage, toothache
- **General disorders and administration site conditions:** chills, infusion site reaction, multi-organ failure, pain
- **Infections and infestations:** influenza, lung infection, rhinitis, 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, intracranial hemorrhage, 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, pulmonary hemorrhage
- **Skin and subcutaneous tissue disorders:** erythema, hyperhidrosis, pruritus
- **Vascular disorders:** deep vein thrombosis, hemorrhage, 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 9 describes Grade 3–4 laboratory abnormalities reported at a rate of ≥ 10% in the KRd arm for patients who received combination therapy.

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Table 9: Grade 3–4 Laboratory Abnormalities (≥ 10% in the KRd Arm) in Cycles 1–12 (20/27 mg/m^2 Regimen In Combination with Lenalidomide and Dexamethasone)

Laboratory Abnormality	KRd (N = 392) n (%)	Rd (N = 389) n (%)
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 dexamethasone; Rd = lenalidomide and dexamethasone

Safety Experience with Kyprolis in Combination with Dexamethasone in Patients with Multiple Myeloma

The safety of Kyprolis in combination with dexamethasone was evaluated in an open-label, randomized trial of patients with relapsed multiple myeloma. The study treatment is described in Section 14.2. Patients received treatment for a median duration of 40 weeks in the Kyprolis/dexamethasone (Kd) arm and 27 weeks in the bortezomib/dexamethasone (Vd) arm.

Deaths due to adverse reactions within 30 days of last study treatment occurred in 22/463 (5%) patients in the Kd arm and 21/456 (5%) patients in the Vd arm. The causes of death occurring in patients (%) in the two arms (Kd *versus* Vd) included cardiac 7 (2%) *versus* 5 (1%), infections 5 (1%) *versus* 8 (2%), disease progression 6 (1%) *versus* 4 (1%), pulmonary 3 (1%) *versus* 2 (< 1%), renal 1 (< 1%) *versus* 0 (0%), and other adverse events 2 (< 1%) *versus* 2 (< 1%). Serious adverse reactions were reported in 48% of the patients in the Kd arm and 36% of the patients in the Vd arm. In both treatment arms, pneumonia was the most commonly reported serious adverse reaction (6% *versus* 9%). Discontinuation due to any adverse reaction occurred in 20% in the Kd arm *versus* 21% in the Vd arm. The most common reaction leading to discontinuation was cardiac failure in the Kd arm (n = 6, 1.3%) and peripheral neuropathy in the Vd arm (n = 19, 4.2%).

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Common Adverse Reactions (≥ 10%)

Adverse reactions in the first 6 months of therapy that occurred at a rate of 10% or greater in the Kd arm are presented in Table 10.

Table 10: Most Common Adverse Reactions (≥ 10% in the Kd Arm) Occurring in Months 1–6 (20/56 mg/m^2 Regimen In Combination with Dexamethasone)

	Kd (N = 463) n (%)		Vd (N = 456) n (%)	
Adverse Reaction by Body System	**Any Grade**	**≥ Grade 3**	**Any Grade**	**≥ Grade 3**
Blood and Lymphatic System Disorders				
Anemia	160 (35)	57 (12)	112 (25)	43 (9)
Thrombocytopenia[a]	127 (27)	46 (10)	112 (25)	65 (14)
Gastrointestinal Disorders				
Diarrhea	111 (24)	14 (3)	150 (33)	26 (6)
Nausea	69 (15)	4 (1)	66 (15)	3 (1)
Constipation	58 (13)	1 (0)	109 (24)	6 (1)
Vomiting	45 (10)	5 (1)	32 (7)	3 (1)
General Disorders and Administration Site Conditions				
Fatigue	112 (24)	13 (3)	124 (27)	25 (6)
Pyrexia	102 (22)	9 (2)	52 (11)	3 (1)
Peripheral edema	75 (16)	3 (1)	73 (16)	3 (1)
Asthenia	71 (15)	9 (2)	66 (14)	13 (3)
Infections and Infestations				
Upper respiratory tract infection	66 (14)	4 (1)	54 (12)	3 (1)
Bronchitis	54 (12)	5 (1)	26 (6)	2 (0)
Nasopharyngitis	45 (10)	0 (0)	42 (9)	1 (0)
Musculoskeletal and Connective Tissue Disorders				
Muscle spasms	66 (14)	1 (0)	22 (5)	3 (1)
Back pain	58 (13)	7 (2)	60 (13)	8 (2)
Nervous System Disorders				
Headache	68 (15)	4 (1)	38 (8)	2 (0)
Peripheral neuropathies[b,c]	54 (12)	7 (2)	167 (37)	23 (5)
Psychiatric Disorders				
Insomnia	103 (22)	5 (1)	113 (25)	10 (2)
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea[d]	123 (27)	23 (5)	66 (15)	8 (2)

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Cough[e]	91 (20)	0 (0)	61 (13)	2 (0)
Vascular Disorders				
Hypertension[f]	80 (17)	29 (6)	33 (7)	12 (3)

Kd = Kyprolis and dexamethasone; Vd = bortezomib and dexamethasone

[a] Thrombocytopenia includes platelet count decreased and thrombocytopenia.

[b] Peripheral neuropathies include peripheral neuropathy, peripheral sensory neuropathy, and peripheral motor neuropathy.

[c] See Clinical Studies (14.2).

[d] Dyspnea includes dyspnea and dyspnea exertional.

[e] Cough includes cough and productive cough.

[f] Hypertension includes hypertension, hypertensive crisis, and hypertensive emergency.

The event rate of ≥ Grade 2 peripheral neuropathy in the Kd arm was 6% (95% CI: 4, 8) *versus* 32% (95% CI: 28, 36) in the Vd arm.

Adverse Reactions Occurring at a Frequency of < 10%

- **Blood and lymphatic system disorders:** febrile neutropenia, leukopenia, lymphopenia, neutropenia, thrombotic microangiopathy, thrombotic thrombocytopenic purpura
- **Cardiac disorders:** atrial fibrillation, cardiac arrest, cardiac failure, cardiac failure congestive, myocardial infarction, myocardial ischemia, palpitations, tachycardia
- **Eye disorders:** cataract, vision blurred
- **Gastrointestinal disorders:** abdominal pain, abdominal pain upper, dyspepsia, gastrointestinal hemorrhage, toothache
- **General disorders and administration site conditions:** chest pain, chills, infusion site reactions (including inflammation, pain, and erythema), pain
- **Hepatobiliary disorders:** cholestasis, hepatic failure, hyperbilirubinemia
- **Immune system disorders:** drug hypersensitivity
- **Infections and infestations:** bronchopneumonia, influenza, lung infection, pneumonia, rhinitis, sepsis, urinary tract infection, viral infection
- **Metabolism and nutrition disorders:** decreased appetite, dehydration, hypercalcemia, hyperkalemia, hyperuricemia, hypoalbuminemia, hypocalcemia, hypomagnesemia, hyponatremia, hypophosphatemia, tumor lysis syndrome
- **Musculoskeletal and connective tissue disorders:** muscular weakness, musculoskeletal chest pain, musculoskeletal pain, myalgia
- **Nervous system disorders:** cerebrovascular accident, dizziness, hypoesthesia, paresthesia, posterior reversible encephalopathy syndrome
- **Psychiatric disorders:** anxiety

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- **Renal and urinary disorders:** renal failure, renal failure acute, renal impairment
- **Respiratory, thoracic and mediastinal disorders:** acute respiratory distress syndrome, dysphonia, epistaxis, interstitial lung disease, oropharyngeal pain, pneumonitis pulmonary embolism, pulmonary edema, pulmonary hypertension, wheezing
- **Skin and subcutaneous tissue disorders:** erythema, hyperhidrosis, pruritus, rash
- **Vascular disorders:** deep vein thrombosis, flushing, hypotension

Laboratory Abnormalities

Table 11 describes Grades 3–4 laboratory abnormalities reported at a rate of ≥ 10% in the Kd arm.

Table 11: Grades 3–4 Laboratory Abnormalities (≥ 10%) in Months 1–6 (20/56 mg/m^2 Regimen In Combination with Dexamethasone)

Laboratory Abnormality	Kd (N = 463) n (%)	Vd (N = 456) n (%)
Decreased lymphocytes	248 (54)	180 (40)
Increase uric acid	243 (53)	198 (43)
Decreased hemoglobin	79 (17)	68 (15)
Decreased platelets	85 (18)	77 (17)
Decreased phosphorus	73 (16)	61 (13)
Decreased creatinine clearance[a]	65 (14)	49 (11)
Increased potassium	55 (12)	21 (5)

Kd = Kyprolis and dexamethasone; Vd = bortezomib and dexamethasone
[a] Calculated using the Cockcroft-Gault formula.

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

The safety of Kyprolis, dosed at 20/27 mg/m^2 by up to 10-minute infusion, 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. Premedication with dexamethasone 4 mg was required before each dose in Cycle 1 and was optional for subsequent cycles. The median age was 64 years (range 32–87), and approximately 57% were male. The patients

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received a median of 5 (range 1–20) prior regimens. The median number of cycles initiated was 4 (range 1–35).

Serious adverse reactions, regardless of causality, were reported in 50% of patients in the pooled Kyprolis monotherapy studies (N = 598). The most common serious adverse reactions 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 reactions was higher in those ≥ 65 years old and those ≥ 75 years old *[see Geriatric Use (8.5)]*.

Deaths due to adverse reactions within 30 days of the last dose of Kyprolis occurred in 30/598 (5%) patients receiving Kyprolis monotherapy. These adverse reactions were related to cardiac disorders in 10 (2%) patients, infections in 8 (1%) patients, renal disorders in 4 (< 1%) patients, and other adverse reactions 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 reaction was acute renal failure (2%).

Safety of Kyprolis monotherapy dosed at 20/56 mg/m^2 by 30-minute infusion was evaluated in a multicenter, open-label study in patients with relapsed and/or refractory multiple myeloma. The study treatment is described in Section 14.3. The patients received a median of 4 (range 1–10) prior regimens.

The common adverse reactions occurring at a rate of 20% or greater with Kyprolis monotherapy are presented in Table 12.

Table 12: Most Common Adverse Reactions (≥ 20%) with Kyprolis Monotherapy

	20/56 mg/m^2 by 30-minute infusion (N = 24)		**20/27 mg/m^2 by 2- to 10-minute infusion (N = 598)**	
Adverse Reaction	**Any Grade n (%)**	**Grades 3 - 5 n (%)**	**Any Grade n (%)**	**Grades 3 - 5 n (%)**

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Fatigue	14 (58)	2 (8)	238 (40)	25 (4)
Dyspnea[a]	14 (58)	2 (8)	202 (34)	21 (4)
Pyrexia	14 (58)	0	177 (30)	11 (2)
Thrombocytopenia	13 (54)	13 (54)	220 (37)	152 (25)
Nausea	13 (54)	0	211 (35)	7 (1)
Anemia	10 (42)	7 (29)	291 (49)	141 (24)
Hypertension[b]	10 (42)	3 (13)	90 (15)	22 (4)
Chills	9 (38)	0	73 (12)	1 (< 1)
Headache	8 (33)	0	141 (24)	7 (1)
Cough[c]	8 (33)	0	134 (22)	2 (< 1)
Vomiting	8 (33)	0	104 (17)	4 (1)
Lymphopenia	8 (33)	8 (33)	85 (14)	73 (12)
Insomnia	7 (29)	0	75 (13)	0
Dizziness	7 (29)	0	64 (11)	5 (1)
Diarrhea	6 (25)	1 (4)	160 (27)	8 (1)
Blood creatinine increased	6 (25)	1 (4)	103 (17)	15 (3)
Peripheral edema	5 (21)	0	118 (20)	1 (< 1)
Back pain	5 (21)	1 (4)	115 (19)	19 (3)
Upper respiratory tract infection	5 (21)	1 (4)	112 (19)	15 (3)
Decreased appetite	5 (21)	0	89 (15)	2 (< 1)
Muscle spasms	5 (21)	0	62 (10)	2 (< 1)
Chest pain	5 (21)	0	20 (3)	1 (< 1)

[a] Dyspnea includes preferred terms of dyspnea and dyspnea exertional.
[b] Hypertension includes hypertension, hypertensive crisis, and hypertensive emergency.
[c] Cough includes cough and productive cough.

Adverse Reactions Occurring at a Frequency of < 20%

- **Blood and lymphatic system disorders:** febrile neutropenia, leukopenia, neutropenia
- **Cardiac disorders:** cardiac arrest, cardiac failure, cardiac failure congestive, myocardial infarction, myocardial ischemia
- **Eye disorders:** cataract, blurred vision
- **Gastrointestinal disorders:** abdominal pain, abdominal pain upper, constipation, dyspepsia, gastrointestinal hemorrhage, toothache
- **General disorders and administration site conditions:** asthenia, infusion site reaction, multi-organ failure, pain
- **Hepatobiliary disorders:** hepatic failure

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- **Infections and infestations:** bronchitis, bronchopneumonia, influenza, lung infection, pneumonia, nasopharyngitis, respiratory tract infection, rhinitis, sepsis, urinary tract infection
- **Metabolism and nutrition disorders:** hypercalcemia, hyperglycemia, hyperkalemia, hyperuricemia, hypoalbuminemia, hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, hypophosphatemia, tumor lysis syndrome
- **Musculoskeletal and connective tissue disorders:** arthralgia, musculoskeletal pain, musculoskeletal chest pain, myalgia, pain in extremity
- **Nervous system disorders:** hypoesthesia, intracranial hemorrhage, paresthesia, peripheral motor neuropathy, peripheral neuropathy, peripheral sensory neuropathy
- **Psychiatric disorders:** anxiety
- **Renal and urinary disorders:** acute renal failure, renal failure, renal impairment
- **Respiratory, thoracic and mediastinal disorders:** dysphonia, epistaxis, oropharyngeal pain, pulmonary edema, pulmonary hemorrhage
- **Skin and subcutaneous tissue disorders:** erythema, hyperhidrosis, pruritus, rash
- **Vascular disorders:** embolic and thrombotic events, venous (including deep vein thrombosis and pulmonary embolism), hemorrhage, 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 13 describes Grade 3–4 laboratory abnormalities reported at a rate of > 10% for patients who received Kyprolis monotherapy.

Table 13: Grade 3–4 Laboratory Abnormalities (> 10%) with Kyprolis Monotherapy

Laboratory Abnormality	Kyprolis 20/56 mg/m^2 (N = 24)	Kyprolis 20/27 mg/m^2 (N = 598)
Decreased lymphocytes	15 (63)	151 (25)
Decreased platelets	11 (46)	184 (31)
Decreased hemoglobin	7 (29)	132 (22)

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Decreased total white blood cell count	3 (13)	71 (12)
Decreased sodium	2 (8)	69 (12)
Decreased absolute neutrophil count	2 (8)	67 (11)

6.2 Postmarketing Experience

The following additional adverse reactions were reported in the postmarketing 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: hemolytic uremic syndrome (HUS), gastrointestinal perforation, pericarditis.

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 can 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. Males of reproductive potential should be advised to avoid fathering a child 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

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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 *[see Use in Specific Populations (8.1)]*. Advise female patients of reproductive potential to use effective contraceptive measures or abstain from sexual activity to prevent pregnancy during treatment with Kyprolis and for at least 30 days following completion of therapy. Advise male patients of reproductive potential to use effective contraceptive measures or abstain from sexual activity to prevent pregnancy during treatment with Kyprolis and for at least 90 days following completion of therapy.

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8.4 Pediatric Use

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

8.5 Geriatric Use

Of 598 patients in clinical studies of Kyprolis monotherapy dosed at 20/27 mg/m^2 by up to 10-minute infusion, 49% were 65 and over, while 16% were 75 and over. 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 (5.1)]*. In a single-arm, multicenter clinical trial of Kyprolis monotherapy dosed at 20/27 mg/m^2 (N = 266), no overall differences in effectiveness were observed between older and younger patients.

Of 392 patients treated with Kyprolis in combination with lenalidomide and dexamethasone, 47% were 65 and over and 11% were 75 years and over. 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 (5.1)]*. No overall differences in effectiveness were observed between older and younger patients.

Of 463 patients treated with Kyprolis dosed at 20/56 mg/m^2 by 30-minute infusion in combination with dexamethasone, 52% were 65 and over and 17% were 75 and over. The incidence of serious adverse events was 44% in patients < 65 years of age, 50% in patients 65 to 74 years of age, and 57% in patients ≥ 75 years of age *[see Warnings and Precautions (5.1)]*. No overall differences in effectiveness were observed between older and younger patients.

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

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

10 OVERDOSAGE

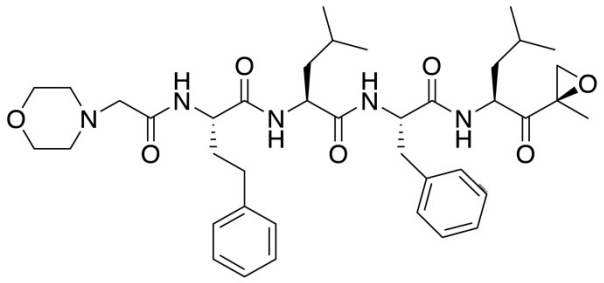
Acute onset of chills, hypotension, renal insufficiency, thrombocytopenia, and lymphopenia has been reported following a dose of 200 mg of Kyprolis administered in error.

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. Kyprolis is a sterile, white to off-white lyophilized powder and is available as a single-dose 30 mg or 60 mg vial. Each 30 mg vial contains 30 mg of carfilzomib, 1500 mg sulfobutylether beta-cyclodextrin, and 28.9 mg anhydrous citric acid and sodium hydroxide for pH adjustment (target pH 3.5). Each 60 mg vial contains 60 mg of carfilzomib, 3000 mg sulfobutylether 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.

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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 mean (CV%) C_{max} and AUC following a 2- to 10-minute intravenous infusion of 27 mg/m^2 of carfilzomib were 4232 ng/mL (49%) and 379 ng•hr/mL (25%), 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.

Following a 30-minute infusion of the 56 mg/m^2 dose, the mean (CV%) AUC of 948 ng•hr/mL (34%) was approximately twice that observed following a 2- to 10-minute infusion at the 27 mg/m^2 dose with a mean (CV%) of 379 ng•hr/mL (25%). The mean (CV%) C_{max} of 2079 ng/mL (44%) following a 30-minute infusion of the 56 mg/m^2 dose was

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lower compared to that of 27 mg/m^2 over the 2- to 10-minute infusion with a mean (CV%) of 4232 ng/mL (49%).

At doses between 20 and 56 mg/m^2, there was a dose-dependent increase in exposure at either infusion duration.

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).

Specific Populations: Clinically significant differences were not observed in the pharmacokinetics of carfilzomib based on age (35-88 years), gender, race, and renal impairment ranging from mild to severe (creatinine clearance < 30 to < 80 mL/min) renal impairment, and chronic dialysis. No dedicated studies have been completed in patients with hepatic impairment, and patients with ALT/AST ≥ 3 × upper limit of normal (ULN) and bilirubin ≥ 2 × ULN were excluded from the Kyprolis clinical trials.

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

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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),

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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 or Refractory Multiple Myeloma (Study 1)

Study 1 was a randomized, open-label, multicenter superiority trial which evaluated the combination of Kyprolis with lenalidomide and dexamethasone (KRd) *versus* lenalidomide and dexamethasone alone (Rd) in patients with relapsed or refractory multiple myeloma who had received 1 to 3 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, not responding to any prior regimen, creatinine clearance < 50 mL/min, ALT/AST > 3.5 × ULN and bilirubin > 2 × ULN, New York Heart Association Class III to IV congestive heart failure, or myocardial infarction within the last 4 months. In the KRd arm, Kyprolis was evaluated at a starting dose of 20 mg/m^2, which was increased to 27 mg/m^2 on Cycle 1, Day 8 onward. Kyprolis was administered as a 10-minute infusion on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle for Cycle 1 through 12. Kyprolis was dosed on Days 1, 2, 15, and 16 of each 28-day cycle from Cycle 13 through 18. Dexamethasone 40 mg was administered orally or intravenously on Days 1, 8, 15 and 22 of each cycle. Lenalidomide was given 25 mg orally on Days 1 to 21 of each 28-day cycle. The Rd treatment arm had the same regimen for lenalidomide and dexamethasone as the KRd treatment arm. Kyprolis 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. Concurrent use of thromboprophylaxis and a

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proton pump inhibitor were required for both arms, and antiviral prophylaxis was required for the KRd arm.

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 14). 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 14: Demographics and Baseline Characteristics in Study 1 (Combination Therapy for Relapsed or Refractory Multiple Myeloma)

Characteristic	KRd Combination Therapy	
	KRd Arm (N = 396)	**Rd Arm (N = 396)**
Age, Median, Years (min, max)	64 (38, 87)	65 (31, 91)
Age ≥ 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 or Not Reported	7 (2)	8 (2)
Number of Prior Regimens, n (%)		
1	184 (46)	157 (40)
2	120 (30)	139 (35)
3[a]	92 (23)	100 (25)
Prior Transplantation	217 (55)	229 (58)
ECOG Performance Status		
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)	153 (39)
III	73 (18)	82 (21)
Unknown	8 (2)	7 (2)
CrCL, mL/min, Median (min, max)	79 (39, 212)	79 (30, 208)
30 to < 50, n (%)	19 (5)	32 (8)
50 to < 80, n (%)	185 (47)	170 (43)

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Refractory to Last Therapy, n (%)	110 (28)	119 (30)
Refractory at Any Time to, n (%):		
Bortezomib	60 (15)	58 (15)
Lenalidomide	29 (7)	28 (7)
Bortezomib + immunomodulatory agent	24 (6)	27 (7)

ECOG = Eastern Cooperative Oncology Group; CrCL = creatinine clearance;
IgG = immunoglobulin G; ISS = International Staging System; KRd = Kyprolis, lenalidomide, and dexamethasone; Rd = lenalidomide and dexamethasone
[a] Including 2 patients with 4 prior regimens.

Patients in the KRd arm demonstrated improved progression-free survival (PFS) compared with those in the Rd arm (HR = 0.69, with 2-sided P-value = 0.0001) as determined using standard 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 in the KRd arm *versus* 17.6 months in the Rd arm (see Table 15 and Figure 1).

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

Table 15: Efficacy Outcomes in Study 1 (Combination Therapy for Relapsed or Refractory Multiple Myeloma)[a]

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

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CI = confidence interval; CR = complete response; KRd = Kyprolis, lenalidomide, and dexamethasone; PFS = progression-free survival; Rd = lenalidomide and dexamethasone; sCR = stringent CR; VGPR = very good partial response

[a] Eligible patients had 1-3 prior lines of therapy.

[b] As determined by an Independent Review Committee.

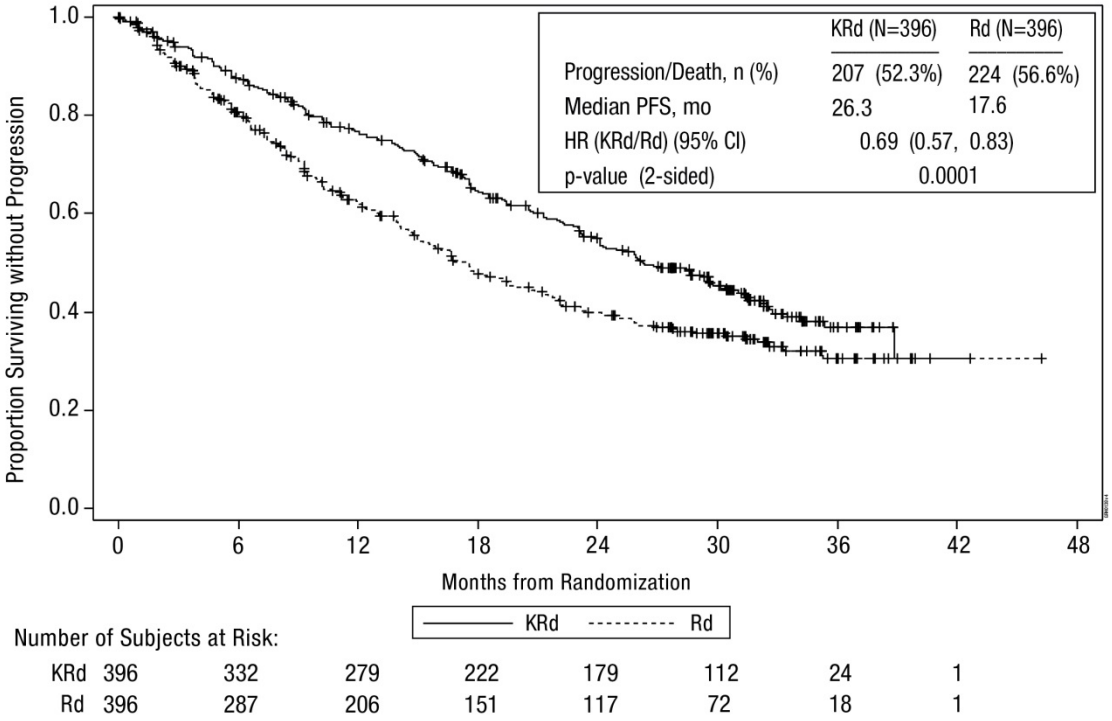
[c] Based on Kaplan Meier estimates.

[d] Based on stratified Cox's model.

[e] The P-value was derived using stratified log-rank test.

The median duration of response (DOR) was 28.6 months (95% CI: 24.9, 31.3) for the 345 patients achieving a response in the KRd arm and 21.2 months (95% CI: 16.7, 25.8) 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 Study 1



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

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

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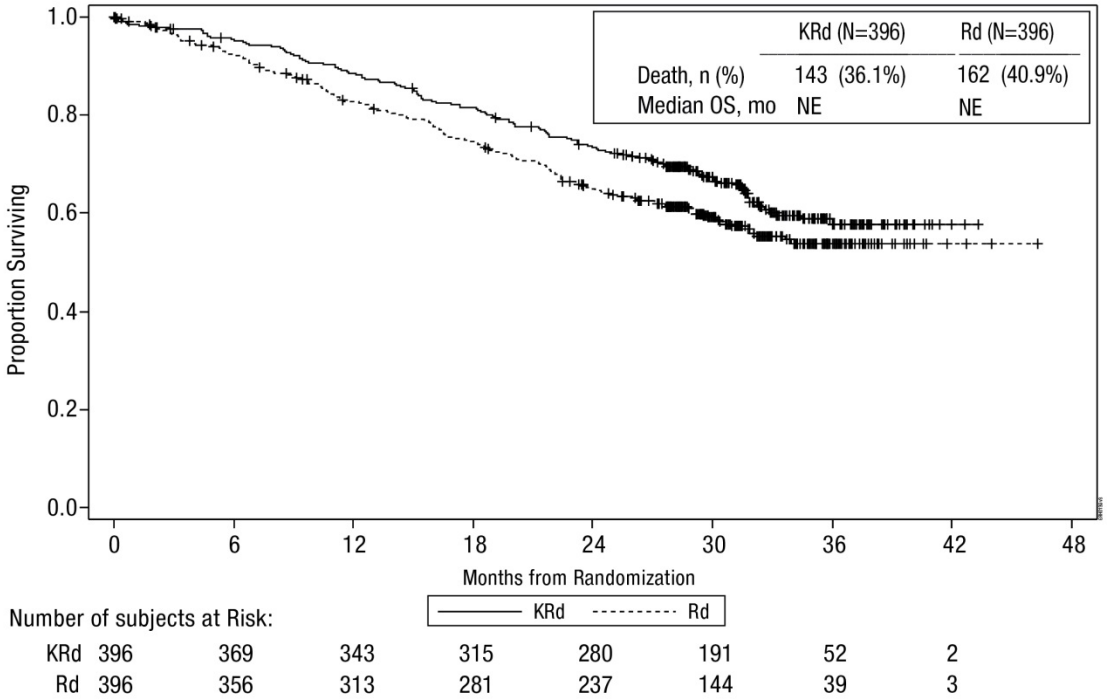
Figure 2: Kaplan-Meier Curve of Interim Overall Survival in Study 1



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

14.2 In Combination with Dexamethasone for the Treatment of Patients with Relapsed or Refractory Multiple Myeloma (Study 2)

Study 2 was a randomized, open-label, multicenter superiority trial of Kyprolis plus dexamethasone (Kd) *versus* bortezomib plus dexamethasone (Vd) in patients with relapsed or refractory multiple myeloma who had received 1 to 3 lines of therapy. A total of 929 patients were enrolled and randomized (464 in the Kd arm; 465 in the Vd arm). Randomization was stratified by prior proteasome inhibitor therapy (yes *versus* no), prior lines of therapy (1 *versus* 2 or 3), current International Staging System stage (1 *versus* 2 or 3), and planned route of bortezomib administration. Patients were excluded if they had less than PR to all prior regimens; creatinine clearance < 15 mL/min; hepatic transaminases ≥ 3 × ULN; or left-ventricular ejection fraction < 40% or other significant cardiac conditions. This trial evaluated Kyprolis at a starting dose of 20 mg/m^2, which was increased to 56 mg/m^2 on Cycle 1, Day 8 onward. Kyprolis was administered twice weekly as a 30-minute infusion on

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Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle. Dexamethasone 20 mg was administered orally or intravenously on Days 1, 2, 8, 9, 15, 16, 22, and 23 of each cycle. In the Vd arm, bortezomib was dosed at 1.3 mg/m^2 intravenously or subcutaneously on Days 1, 4, 8, and 11 of a 21-day cycle, and dexamethasone 20 mg was administered orally or intravenously on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each cycle. Concurrent use of thromboprophylaxis was optional, and prophylaxis with an antiviral agent and proton pump inhibitor was required. Of the 465 patients in the Vd arm, 381 received bortezomib subcutaneously. Treatment continued until disease progression or unacceptable toxicity.

The demographics and baseline characteristics are summarized in Table 16.

Table 16: Demographics and Baseline Characteristics in Study 2 (Combination Therapy for Relapsed or Refractory Multiple Myeloma)

Characteristics	Kd Arm (N = 464)	Vd Arm (N = 465)
Age, Years		
Median (min, max)	65 (35, 89)	65 (30, 88)
< 65, n (%)	223 (48)	210 (45)
65–74, n (%)	164 (35)	189 (41)
≥ 75, n (%)	77 (17)	66 (14)
Sex, n (%)		
Female	224 (48)	236 (51)
Male	240 (52)	229 (49)
Race, n (%)		
White	348 (75)	353 (76)
Black	8 (2)	9 (2)
Asian	56 (12)	57 (12)
Other or Not Reported	52 (11)	46 (10)
ECOG Performance Status, n (%)		
0	221 (48)	232 (50)
1	211 (46)	203 (44)
2	32 (7)	30 (6)
Creatinine Clearance (mL/min)		
Median (min, max)	73 (14, 185)	72 (12, 208)
< 30, n (%)	28 (6)	28 (6)
30 – < 50, n (%)	57 (12)	71 (15)

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50 – < 80, n (%)	186 (40)	177 (38)
≥ 80, n (%)	193 (42)	189 (41)
FISH, n (%)		
High-risk	97 (21)	113 (24)
Standard-risk	284 (61)	291 (63)
Unknown-risk	83 (18)	61 (13)
ISS Stage at Study Baseline, n (%)		
ISS I	212 (46)	205 (44)
ISS II	138 (30)	151 (33)
ISS III	114 (25)	109 (23)
Number of Prior Regimens		
1	232 (50)	232 (50)
2	157 (34)	145 (31)
3	75 (16)	87 (19)
4	0 (0)	1 (0)
Prior Therapies, n (%)	464 (100)	465 (100)
Bortezomib	250 (54)	252 (54)
Transplant for Multiple Myeloma	266 (57)	272 (59)
Thalidomide	211 (46)	247 (53)
Lenalidomide	177 (38)	177 (38)
Bortezomib + immunomodulatory agent	158 (34)	167 (36)
Refractory to last prior therapy, n (%)[a]	184 (40)	188 (40)

ECOG = Eastern Cooperative Oncology Group; FISH = Fluorescence in situ hybridization; ISS = International Staging System; Kd = Kyprolis plus dexamethasone; Vd = bortezomib and dexamethasone
[a] Refractory = disease not achieving a minimal response or better, progressing during therapy, or progressing within 60 days after completion of therapy.

The efficacy of Kyprolis was evaluated by PFS as determined by an IRC using IMWG response criteria. The trial showed a median PFS of 18.7 months in the Kd arm *versus* 9.4 months in the Vd arm (see Table 17 and Figure 3).

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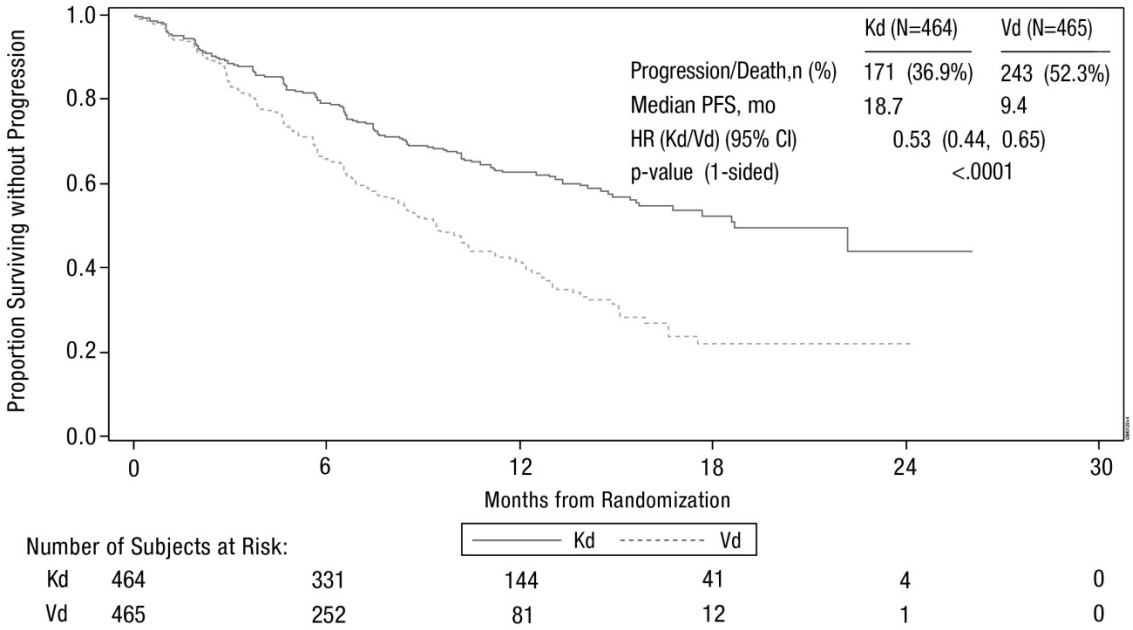
Figure 3: Kaplan-Meier Plot of Progression-Free Survival in Study 2



HR = hazard ratio; Kd = Kyprolis plus dexamethasone; PFS = progression-free survival; Vd = bortezomib and dexamethasone

Other endpoints included OS and overall response rate (ORR). At the time of analysis, OS data were not mature. ORR was 77% for patients in the Kd arm and 63% for patients in the Vd arm (see Table 17).

Table 17: Summary of Key Results in Study 2 (Intent-to-Treat Population)[a]

	Kd Arm (N = 464)	**Vd Arm (N = 465)**
PFS[b]		
Median[c], Months (95% CI)	18.7 (15.6, —)	9.4 (8.4, 10.4)
Hazard Ratio (Kd/Vd) (95% CI)[d]	0.53 (0.44, 0.65)	
P-value (1-sided)[e]	< 0.0001	
Overall Response[b]		
N with Response	357	291
ORR (%) (95% CI)[f]	77 (73, 81)	63 (58, 67)
P-value (1-sided)[g]	< 0.0001	
Response Category, n (%)		
sCR	8 (2)	9 (2)

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CR	50 (11)	20 (4)
VGPR	194 (42)	104 (22)
PR[h]	105 (23)	158 (34)

CI = confidence interval; CR = complete response; Kd = Kyprolis and dexamethasone; ORR = overall response rate; PFS = progression-free survival; sCR = stringent CR; Vd = bortezomib and dexamethasone; VGPR = very good partial response
[a] Eligible patients had 1-3 prior lines of therapy.
[b] PFS and ORR were determined by an Independent Review Committee.
[c] Based on Kaplan Meier estimates.
[d] Based on a stratified Cox's model.
[e] The P-value was derived using stratified log-rank test.
[f] Exact confidence interval.
[g] The P-value was derived using Cochran Mantel Haenszel test.
[h] Includes one patient in each arm with a confirmed PR which may not have been the best response.

The median DOR in subjects achieving PR or better was 21.3 months (95% CI: 21.3, not estimable) in the Kd arm and 10.4 months (95% CI: 9.3, 13.8) in the Vd arm. The median time to response was 1 month (range < 1 to 8 months) in both arms.

14.3 Monotherapy for the Treatment of Patients with Relapsed or Refractory Multiple Myeloma (Study 3, Study 4, and Study 5)

Study 3

Study 3 was a multicenter, open-label, dose escalation, single-arm trial that evaluated the safety of carfilzomib monotherapy as a 30-minute infusion in patients with relapsed or refractory multiple myeloma after 2 or more lines of therapy. Patients were excluded if they had a creatinine clearance < 20 mL/min; ALT ≥ 3 × upper limit of normal (ULN), bilirubin ≥ 1.5 × ULN; New York Heart Association class III or IV congestive heart failure; or other significant cardiac conditions. A total of 24 subjects with multiple myeloma were enrolled at the maximum tolerated dose level of 20/56 mg/m^2. Carfilzomib was administered twice-weekly for 3 consecutive weeks (Days 1, 2, 8, 9, 15, and 16) of a 28-day cycle. In Cycle 13 onward, the Day 8 and 9 carfilzomib doses could be omitted. Patients received carfilzomib at a starting dose of 20 mg/m^2 on Days 1 and 2 of Cycle 1, which was increased to 56 mg/m^2 for all subsequent doses. Dexamethasone 8 mg orally or intravenously was required prior to each carfilzomib dose in Cycle 1 and was optional in subsequent cycles. Treatment was continued until disease progression or unacceptable toxicity.

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Efficacy was evaluated by ORR and DOR. ORR by investigator assessment was 50% (95% CI: 29, 71) per IMWG criteria (see Table 18). The median DOR in subjects who achieved a PR or better was 8.0 months (Range: 1.4, 32.5).

Table 18: Response Categories in Study 3 (20/56 mg/m^2 Monotherapy Regimen)

Characteristic	Study Patients[a] n (%)
Number of Patients (%)	24 (100)
Overall Response[b]	12 (50)
95% CI[c]	(29, 71)
Response Category	
sCR	1 (4)
CR	0 (0)
VGPR	4 (17)
PR	7 (29)

sCR = stringent complete response; VGPR = very good partial response
[a] Eligible patients had 2 or more prior lines of therapy.
[b] Per investigator assessment.
[c] Exact confidence interval.

Study 4

Study 4 was a single-arm, multicenter clinical trial of Kyprolis monotherapy by up to 10-minute infusion. Eligible patients were those with relapsed and refractory multiple myeloma who had received at least two prior therapies (including bortezomib and thalidomide and/or lenalidomide) and had ≤ 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 had a total bilirubin ≥ 2 × ULN; creatinine clearance < 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 up to 10 minutes on two consecutive days each week for three weeks, followed by a 12-day rest period (28-day treatment cycle), until

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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 19.

Table 19: Demographics and Baseline Characteristics in Study 4 (20/27 mg/m^2 Monotherapy Regimen for Relapsed and Refractory Multiple Myeloma)

Characteristic	Number of Patients (%)
Patient Characteristics	
Enrolled patients	266 (100)
Median age, years (range)	63 (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)	5.4 (0.5, 22.3)
Plasma cell involvement (< 50% / ≥ 50% / unknown)	143 (54) / 106 (40) / 17 (6)
ISS Stage at Study Baseline	
I	76 (29)
II	102 (38)
III	81 (31)
Unknown	7 (3)
Cytogenetics or FISH analyses	
Normal/Favorable	159 (60)
Poor Prognosis	75 (28)
Unknown	32 (12)
Creatinine clearance < 30 mL/min	6 (2)

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FISH = Fluorescence in situ hybridization; ISS = International Staging System
[a] Range: 1, 20.
[b] Categories for refractory status are derived by programmatic assessment using available laboratory data.

Efficacy was evaluated by ORR as determined by IRC assessment using IMWG criteria. The median number of cycles started was four. The ORR (PR or better) was 23% (95% CI: 18, 28) (see Table 20). The median DOR was 7.8 months (95%CI: 5.6, 9.2).

Table 20: Response Categories in Study 4 (20/27 mg/m^2 Monotherapy Regimen)

Characteristic	Study Patients[a] n (%)
Number of Patients (%)	266 (100)
Overall Response[b]	61 (23)
95% CI[c]	(18, 28)
Response Category	
CR	1 (< 1)
VGPR	13 (5)
PR	47 (18)

CR = complete response; VGPR = very good partial response
[a] Eligible patients had 2 or more prior lines of therapy and were refractory to the last regimen.
[b] As assessed by the Independent Review Committee.
[c] Exact confidence interval.

Study 5

Study 5 was a single-arm, multicenter clinical trial of Kyprolis monotherapy by up to 10-minute infusion. Eligible patients were those with relapsed or refractory multiple myeloma who were bortezomib-naïve, had received one to three prior lines of therapy and had ≤ 25% response or progression during therapy or within 60 days after completion of therapy. Patients were excluded from the trial if they were refractory to standard first-line therapy or had a total bilirubin ≥ 2 × ULN; creatinine clearance < 30 mL/min; New York Heart Association Class III to IV congestive heart failure; symptomatic cardiac ischemia; myocardial infarction within the last 6 months; active infections requiring treatment; or pleural effusion.

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Kyprolis was administered intravenously up 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 70 patients were treated with this 20/27 mg/m^2 regimen. Baseline patient and disease characteristics are summarized in Table 21.

Table 21: Demographics and Baseline Characteristics in Study 5 (20/27 mg/m^2 Monotherapy Regimen for Relapsed or Refractory Multiple Myeloma)

Characteristic	Number of Patients (%)
Patient Characteristics	
Enrolled patients	70 (100)
Median age, years (range)	66 (45, 85)
Age group, < 65 / ≥ 65 (years)	31 (44) / 39 (56)
Gender (male / female)	44 (63) / 26 (37)
Race (White / Black / Asian / Hispanic / Other)	52 (74) / 12 (17) / 3 (4) / 2 (3) / 1 (1)
Disease Characteristics	
Number of Prior Regimens (median)	2[a]
Prior Transplantation	47 (67)
Refractory Status to Most Recent Therapy[b]	
Refractory: Progression during most recent therapy	28 (40)
Refractory: Progression within 60 days after completion of most recent therapy	7 (10)
Refractory: ≤ 25% response to treatment	10 (14)
Relapsed: Progression after 60 days post treatment	23 (33)
No Signs of Progression	2 (3)
Years since diagnosis, median (range)	3.6 (0.7, 12.2)
Plasma cell involvement (< 50% / ≥ 50% / unknown)	54 (77) / 14 (20) / 1 (1)
ISS Stage at Study Baseline, n (%)	
I	28 (40)
II	25 (36)
III	16 (23)
Unknown	1 (1)
Cytogenetics or FISH analyses	
Normal/Favorable	57 (81)

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Poor Prognosis	10 (14)
Unknown	3 (4)
Creatinine clearance < 30 mL/min	1 (1)

FISH = Fluorescence in situ hybridization; ISS = International Staging System
[a] Range: 1, 4.
[b] Categories for refractory status are derived by programmatic assessment using available laboratory data.

Efficacy was evaluated by ORR as determined by IRC assessment using IMWG criteria. The median number of cycles started was seven. The ORR (PR or better) was 50% (95% CI: 38, 62) (see Table 22). The median DOR was not reached.

Table 22: Response Categories in Study 5 (20/27 mg/m^2 Monotherapy Regimen)

Characteristic	Study Patients[a] n (%)
Number of Patients (%)	70 (100)
Overall Response[b]	35 (50)
95% CI[c]	(38 - 62)
Response Category	
CR	1 (1)
VGPR	18 (26)
PR	16 (23)

CR = complete response; VGPR = very good partial response
[a] Eligible patients had 1-3 prior lines of therapy and were refractory to the last regimen.
[b] As assessed by an Independent Review Committee.
[c] Exact confidence interval.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Kyprolis (carfilzomib) is supplied as:

- An individually packaged single-dose vial containing 30 mg of carfilzomib as a white to off-white lyophilized cake or powder: NDC 76075-102-01.
- An individually packaged single-dose vial containing 60 mg of carfilzomib as a white to off-white lyophilized cake or powder: NDC 76075-101-01.

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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:

Cardiac Toxicities: Advise patients of the risks and symptoms of cardiac failure and ischemia *[see Warnings and Precautions (5.1)]*.

Dehydration: 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 dehydration *[see Warnings and Precautions (5.3)]*.

Respiratory: Advise patients that they may experience cough or shortness of breath (dyspnea) during treatment with Kyprolis. This most commonly occurs within a day of dosing. Advise patients to contact their physician if they experience shortness of breath *[see Warnings and Precautions (5.6)]*.

Venous Thrombosis: Inform patients of the risk of venous thromboembolism and discuss the options for prophylaxis. Advise patients to seek immediate medical attention for symptoms of venous thrombosis or embolism *[see Warnings and Precautions (5.8)]*.

Infusion Reactions: Advise patients of the risk of infusion reactions, and discuss the common signs and symptoms of infusion reactions with the patients *[see Warnings and Precautions (5.9)]*.

Bleeding: Inform patients that they may bruise or bleed more easily or that it may take longer to stop bleeding and to report to their physician any prolonged, unusual or excessive bleeding. Instruct patients on the signs of occult bleeding *[see Warnings and Precautions (5.10)]*.

Hepatic: Inform patients of the risk of developing hepatic failure. Advise patients to contact their physician if they experience jaundice *[see Warnings and Precautions (5.12)]*.

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Other: Inform patients to contact their physician if they experience neurologic symptoms such as headaches, confusion, seizures, or visual loss *[see Adverse Reactions (6) and Warnings and Precautions (5)]*.

Driving/Operating Machines: 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 *[see Adverse Reactions (6)]*.

Pregnancy/Nursing: Counsel females of reproductive potential to use effective contraceptive measures to prevent pregnancy during and for at least 30 days after treatment with Kyprolis. Counsel males of reproductive potential to use effective contraceptive measures to prevent pregnancy during and for at least 90 days after treatment with Kyprolis. Advise the patient to contact their physician immediately if pregnancy does occur during these times. 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 *[see Warnings and Precautions (5.15) and Use in Specific Populations (8.1, 8.3)]*.

Concomitant Medications: 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.

AMGEN®

Kyprolis® (carfilzomib)

Manufactured for:
Onyx Pharmaceuticals, Inc.
Thousand Oaks, CA 91320-1799 U.S.A
Patent: http://pat.amgen.com/kyprolis

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